The American Journal of

# CARDIOLOGY

OFFICIAL JOURNAL OF THE American College of Cardiology

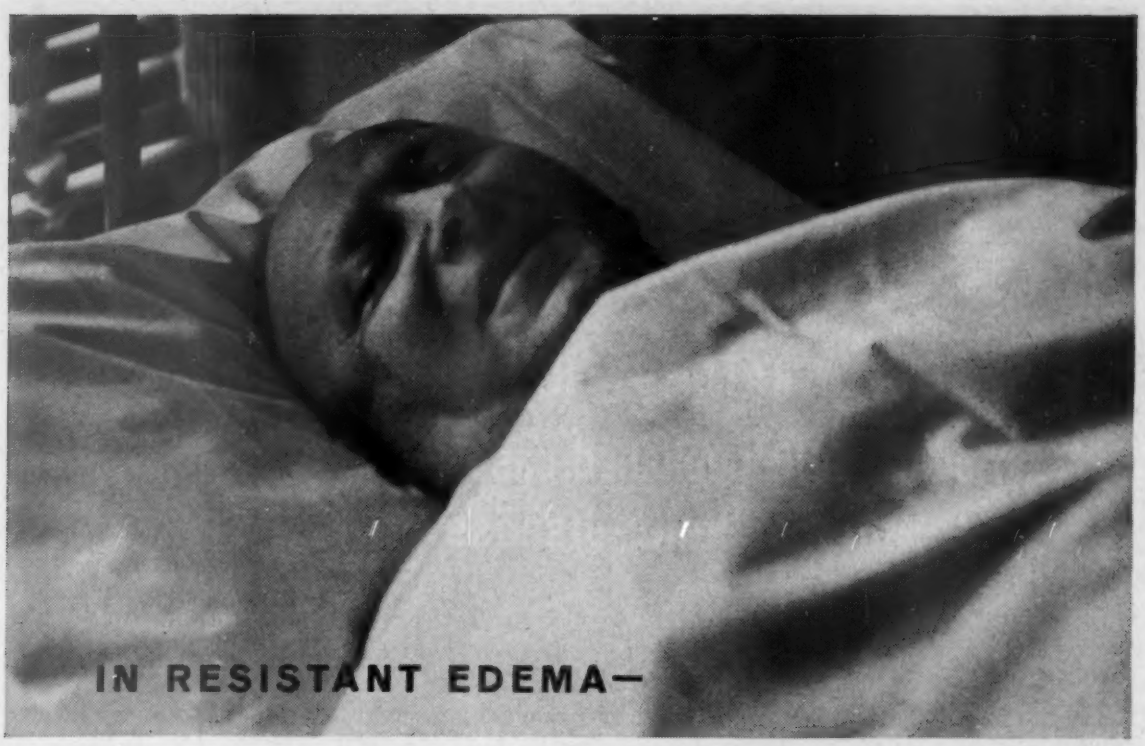
## Calcium and the Electrocardiogram



**INDEX ISSUE**

A PUBLICATION OF THE Yorke GROUP

JUNE 1961




# ALDACTAZIDE®

(brand of spironolactone with hydrochlorothiazide)

• restores dry weight • ambulates the patient

When patients require maximal control of edema and ascites, Aldactazide will frequently free them from excess fluid when no other drug or combination of drugs will do so adequately.

The two components of Aldactazide—Aldactone®, brand of spironolactone, and hydrochlorothiazide—activate diuresis by two different mechanisms in two different sites of the renal tubules. This separate and dual influence increases diuresis not merely by additive but by truly synergistic increments.

Further, by protecting potassium reserves, Aldactazide provides optimal safety when therapy must be prolonged.

With Aldactazide many of your patients can lead more normal lives, in greater comfort with less restricted activity, free from the burden of edema and ascites.

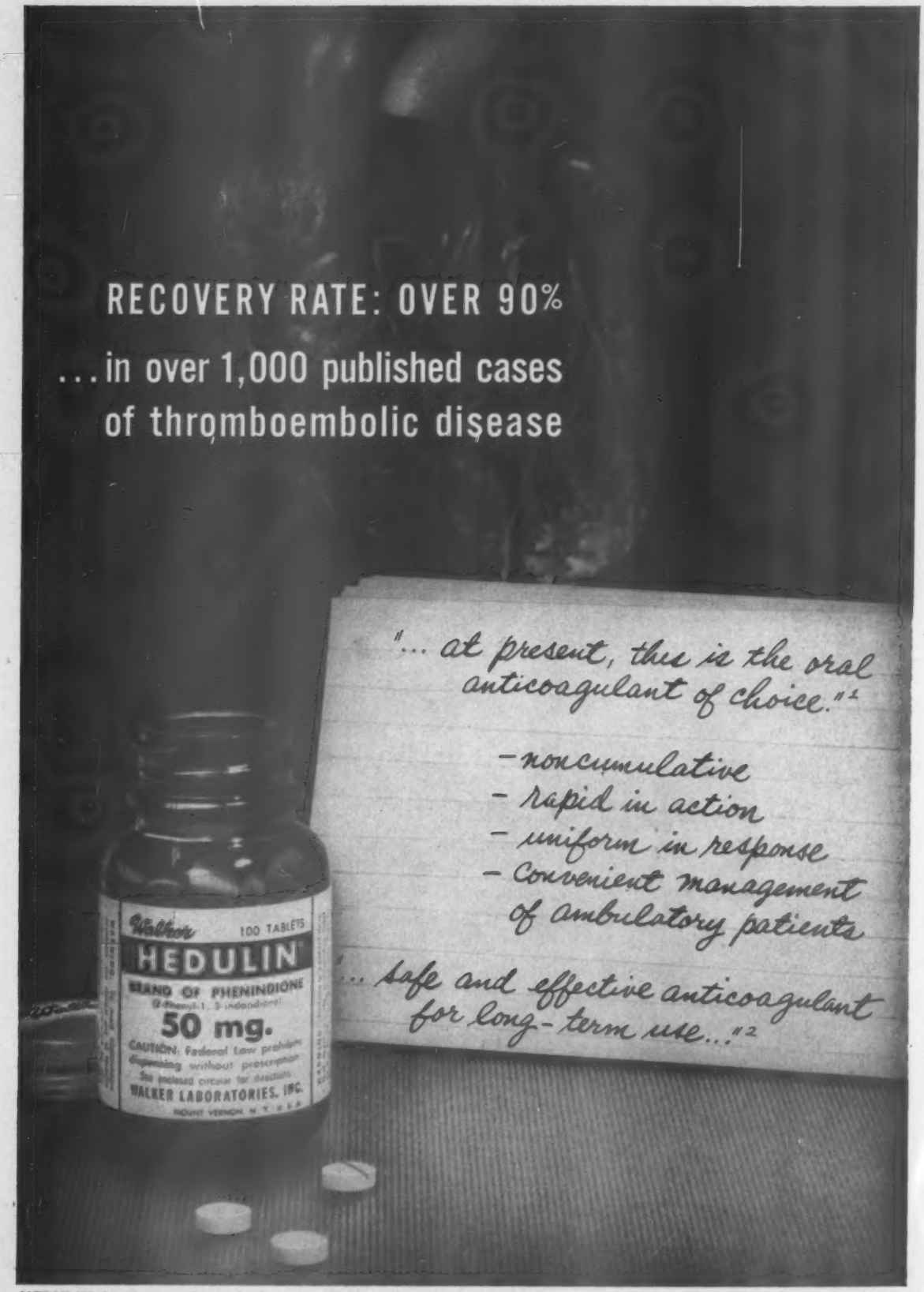
## INDICATIONS:

Edema of congestive heart failure, cirrhotic edema and ascites, edema of nephrosis, idiopathic edema.

The usual adult dosage of Aldactazide is one tablet four times daily, although dosage may range from one to eight tablets daily.

Aldactazide is supplied as compression-coated white tablets, each tablet containing 75 mg. of Aldactone and 25 mg. of hydrochlorothiazide.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS
*Research in the Service of Medicine*




**HEDULIN** is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

**1.** Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. **2.** Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

Symbol of Distinguished Journalism

# The American Journal of Cardiology



THE AMERICAN JOURNAL OF CARDIOLOGY is published monthly by The Reuben H. Donnelley Corporation, Executive and Editorial Offices, 466 Lexington Avenue, New York 17, N. Y. June 1961, Volume 7, No. 6.  Publication Office, 20th and Northampton Streets, Easton, Pa. Second-class postage paid at Easton, Pa. Official Journal of the American College of Cardiology.

SUBSCRIPTIONS: United States $12.00 a year; Canada $13.00; Foreign $15.00
SINGLE COPIES: Regular Issues $2.00; Symposium and Special Issues $4.00

MAIL CHANGES OF ADDRESS AND SUBSCRIPTION ORDERS TO: The American Journal of Cardiology, 466 Lexington Avenue, New York 17, N. Y. Change of address must reach us one month in advance.

MANUSCRIPTS: All manuscripts should be typewritten double space and submitted in duplicate to the Editorial Office of The American Journal of Cardiology, 466 Lexington Avenue, New York 17, N. Y. The top should be indicated on the back of each photograph. Reference style: Smith, J. S. Treatment of cardiac failure. *Am. J Cardiol.*, 3: 274, 1959.

AMERICAN COLLEGE OF CARDIOLOGY: All communications for the College should be addressed to the American College of Cardiology, Office of the Executive Director, 350 Fifth Ave., New York 1, N. Y.

PLINY A. PORTER—Publisher
JOHN J. MARTIN—Assistant Publisher

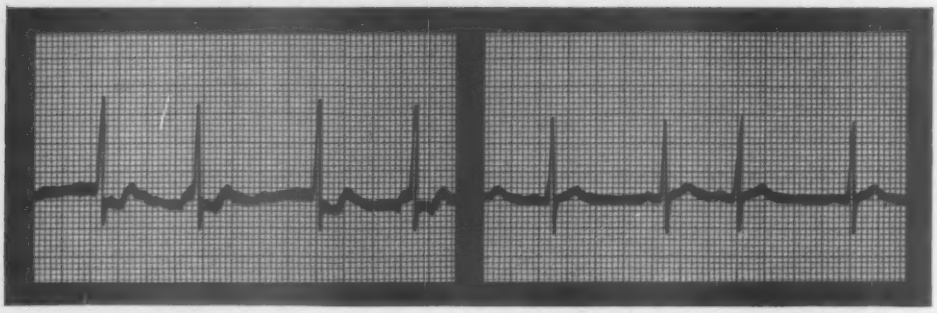
# coronary artery disease is not limited to angina

## ...neither is Peritrate

**In postcoronary patients with or without angina, Peritrate provides the benefits of substantial and sustained increase in myocardial blood flow without significant change in cardiac output, blood pressure or pulse rate.**

electrocardiographic evidence in

**a patient with angina***

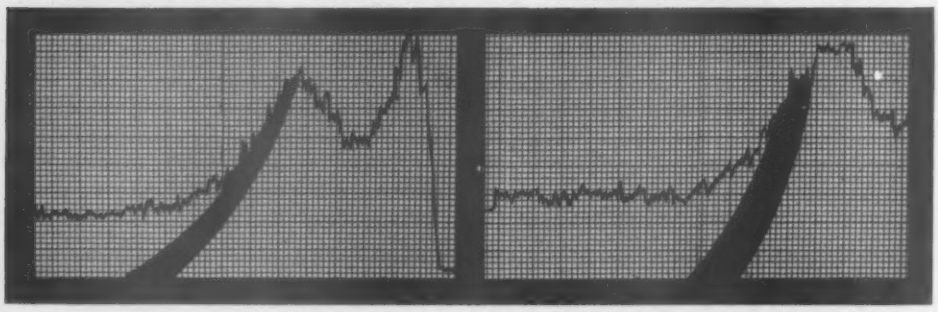


**Before Peritrate**—S-T segment depressed after standard exercise.

**After Peritrate** (20 mg. given 4 hours before exercise test) S-T segment now normal.

radioisotopic tracings of

**a postcoronary patient without angina***



**Before Peritrate**—Radioisotopic tracing shows reduced myocardial blood flow (shaded area) after infarction.

**After Peritrate** (20 mg. given 2½ hours before study) myocardial blood flow substantially increased.

**Full dosage information, available on request, should be consulted before initiating therapy.**

***Electrocardiograms, radioisotopic tracings and case histories on file in the Medical Department, Warner-Chilcott Laboratories**

basic therapy in coronary artery disease
—with or without angina

# Peritrate®

**brand of pentaerythritol tetranitrate**

EP1A

WARNER CHILCOTT

MORRIS PLAINS, N.J.

**makers of Tedral Gelusil Proloid Mandelamine**

# The American Journal of Cardiology

Volume VII JUNE 1961 Number 6

## CONTENTS

## *Clinical Studies*



## *Experimental Studies*



*Contents continued on page 7*

# Proven

in over six years of clinical use and
more than 750 published clinical studies

# Effective

for relief of anxiety and tension

# Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
3. does not produce ataxia, change in appetite or libido
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not impair mental efficiency or normal behavior

# Miltown®

meprobamate (Wallace)

*Usual dosage:* One or two 400 mg. tablets t.i.d.
*Supplied:* 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

*Also supplied in sustained-release capsules . . .*

**Meprospan®**

Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4294

WALLACE LABORATORIES / *Cranbury, N. J.*

# *CONTENTS continued—June 1961*

VOLUME SEVEN NUMBER SIX



## *Review*



## *Historical Milestones*



*Contents continued on page 9*

# New Alvodine ethanesulfonate

trademark

Brand of piminodine ethanesulfonate

## Analgesic potency as great as morphine without drowsiness or hypnosis*

Alvodine, a new and powerful narcotic analgesic, relieves pain as effectively as morphine, yet is much safer because it is free from the high incidence and severity of morphine's side effects. Alvodine is effective *orally* as well as parenterally. Alvodine causes almost no sedation, drowsiness or euphoria. Respiratory and circulatory depression are rare with customary doses; nausea and vomiting are uncommon. Constipation has not been reported.

***Preferred agent for specific situations***

Alvodine is especially well suited for *postoperative analgesia* because it permits most patients to remain alert and at the same time free from pain. The risk of postoperative pulmonary hypostasis and venous stagnation is decreased because the use of Alvodine allows patients to be mobilized sooner.

Alvodine is ideal for *ambulatory* and *semiambulatory patients* who are in need of strong analgesia. Patients with cancer remain alert and can often carry on their normal daily activities when freed of pain by *oral* doses of Alvodine.

*Dosage:* Orally, from 25 to 50 mg. every four to six hours as required. By subcutaneous or intramuscular injection, from 10 to 20 mg. every four hours as required.

*How Supplied:* Alvodine tablets, 50 mg., scored. Alvodine ampuls, 1 cc., containing 20 mg. per cc. *Narcotic Blank Required.*

Winthrop LABORATORIES
New York 18, N. Y.

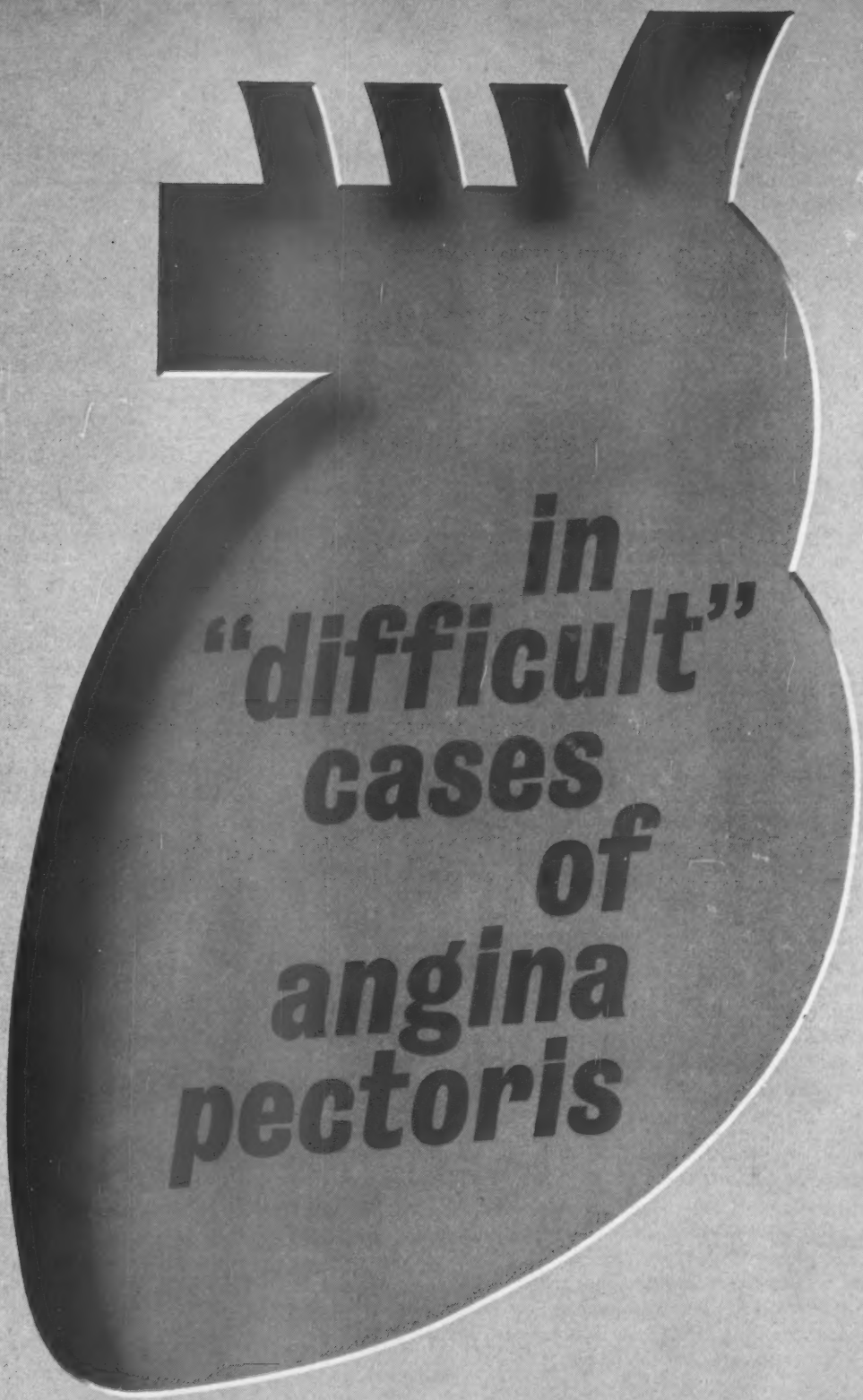
Write for Alvodine brochure containing detailed information on clinical experience, addiction liability, side effects and precautions.

*In more than 90% of patients.

## *Case Reports*



*Contents continued on page 11*



# in "difficult" cases of angina pectoris

# Marplan

***prevents anginal pain[1-4]***
***increases exercise tolerance[2,5,6]***
***reduces nitroglycerin requirements[2,3]***

A potent regulator of amine oxidase, Marplan has demonstrated a high degree of effectiveness in moderately severe to intractable angina pectoris. Improvement on Marplan ranged from a reduction in the number of attacks to virtual abolition of the anginal state. With Marplan, anginal relief is enhanced by a more confident mental climate — improving the chances of success of the entire prophylactic regimen. However, since the precise manner in which Marplan improves the cardiac status is as yet undefined, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy. Consult literature and dosage information, available on request, before prescribing.

**References:** 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, **Virginia M. Month.**, 87:23, 1960. 4. T. Winsor and P. Zarco, **Angiology**, 11: (Part 2), 67, 1960. 5. G. C. Griffith, **Clin. Med.**, 6:1555, 1959. 6. G. C. Griffith, **Dis. Nerv. System**, 21 (Suppl.), 101, 1960.

MARPLAN® — 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine

ROCHE
ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.

# *CONTENTS continued—June 1961*

VOLUME SEVEN NUMBER SIX

## *Diagnostic Shelf*



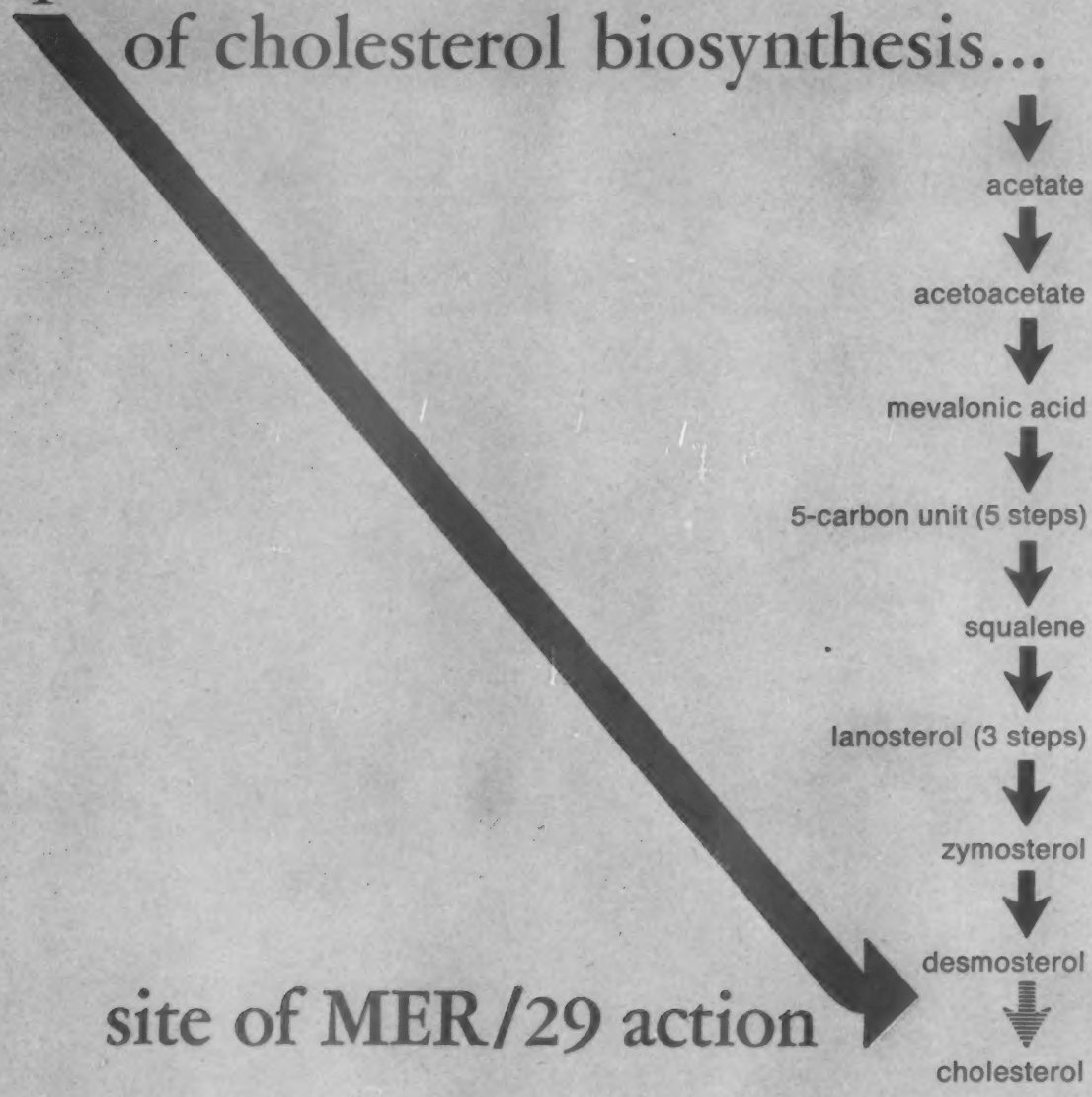
## *Special Departments*



*Index to Advertisers on pages 55 and 56*

HOW MER/29 DIFFERS FROM OTHER CHOLESTEROL-LOWERING MEASURES

# specific[1], demonstrated[2] inhibition[3] of cholesterol biosynthesis...




**1.** The primary, the *only* known action of MER/29 is to lower the total body pool of sterols (serum and tissue); no effect on any other system or organ reported to date.

**2.** "Using each patient as his own control, the peak *total* sterol radioactivity after injection of mevalonic acid-2-$C^{14}$ was compared on and off MER/29. As much as a 50 per cent inhibition on MER/29 was observed in some patients."
—Steinberg, D.; Avigan, J., and Feigelson, E. B.: Circulation 22:663 (Oct.) 1960.

**3.** "Studies of lipid metabolism have stressed the importance of cholesterol biosynthesis, as opposed to cholesterol intake, in determining cholesterol balance."
—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

# ...leading to specific, demonstrated advantages in cholesterol-lowering therapy

particularly in patients with coronary artery disease, generalized atherosclerosis, and other conditions thought to be associated with abnormal cholesterol metabolism

**MER/29 REDUCES CHOLESTEROL IN AS MANY AS 8 OUT OF 10 PATIENTS:** MER/29 reduces both serum and tissue cholesterol without strict adherence to diet. Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

**CONCURRENT BENEFITS REPORTED IN SOME PATIENTS:** In patients with coronary artery disease, some of the concurrent benefits reported include decreased incidence and severity of anginal attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

**MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY:** Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity and other conditions associated with cardiovascular disorders. These include nitroglycerin, PETN, and anticoagulants.

CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is *contraindicated in pregnancy.*

DOSAGE: One 250 mg. capsule daily, before breakfast.

SUPPLIED: Bottles of 30 pearl gray capsules.
Complete bibliography and product information available on request.

# MER/29

(triparanol)

Merrell
SINCE 1828

*The Wm. S. Merrell Company*
*Division of Richardson-Merrell Inc.*
*Cincinnati, Ohio • Weston, Ontario*

Trademark: MER/29®

# PUBLISHER'S INFORMATION PAGE

The Editors and Publishers of **THE AMERICAN JOURNAL OF CARDIOLOGY** welcome concise articles on new findings in cardiology. As is customary in professional publications, statements in articles are the responsibility of the authors; articles must be contributed solely to **THE AMERICAN JOURNAL OF CARDIOLOGY**; material is copyrighted and may not be reproduced without permission of the publishers.

## *Preparation of Manuscripts*

Authors are requested to follow these instructions carefully in preparing manuscripts: Please double space with good margins; type on one side of the sheet only; make a carbon copy for yourself and send the original with one carbon copy to the editor; include staff position and connection; list bibliographic references in chronological order as referred to in text at the end of the article (not in footnotes). Please make certain each reference contains the name of author with initials; title of article; name of periodical with volume, page and year. For example: Smith, J. S. Treatment of cardiac failure. *Am. J. Cardiol.*, 3:274, 1959.

## *Preparation of Illustrations*

So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

Type legends for illustrations on a separate sheet with numbers corresponding to those on the photographs or drawings. Please do not attach legends to the pictures.

A reasonable number of illustrations are supplied free of cost; we know the authors will understand that special arrangements must be made with the publishers for excess illustrations and tables.

## *Reviews, Abstracts*

Books for review may be sent directly to the Editor, Simon Dack, M.D., **The American Journal of Cardiology**, 466 Lexington Avenue, New York 17.

Permission to abstract must be obtained from the publisher. Only paid circulation journals will be permitted to abstract.

## *Reprints*

Orders for reprints of articles should be sent directly to the Publisher, **The American Journal of Cardiology**, 466 Lexington Avenue, New York 17, N. Y. Prices are quoted after articles are published.

**The American Journal of Cardiology**

466 Lexington Avenue, New York 17, New York

# DRAMATIC
*physical and emotional relief in*
# ANGINA PECTORIS

**'round-the-clock protection against both pain and fear**

# COROVAS

**Tymcaps**

COROVAS is a nontoxic, uniform-acting, long-acting vasodilator to control or prevent attacks of angina pectoris. One COROVAS Tymcap upon arising provides up to 12 hours of continuous coronary vasodilation, and another COROVAS Tymcap before the evening meal affords maximum protection against seizures all night. COROVAS alleviates the associated fear of pain. Reduces the need for emergency nitroglycerin. Safe and effective for long-term therapy.

**SUPPLIED**—Boxes of 60 and 120.

**PROLONGED, SUSTAINED ACTION OF VASODILATING PENTAERYTHRITOL TETRANITRATE (PETN) 30 MG., AND SEDATIVE SECOBARBITURIC ACID 50 MG. IN EACH COROVAS TYMCAP.**
As with all nitrates, use with caution in glaucoma.

**AMFRE GRANT, INC.**
Brooklyn 26, N. Y.

# Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

**REFERENCES:** 1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

**Supplied:** Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

**Dosage:** 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

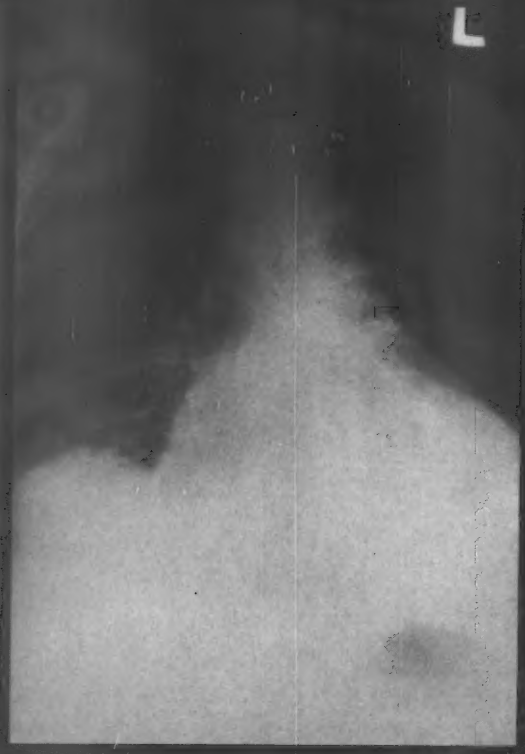
CML-3619

# Miltrate®

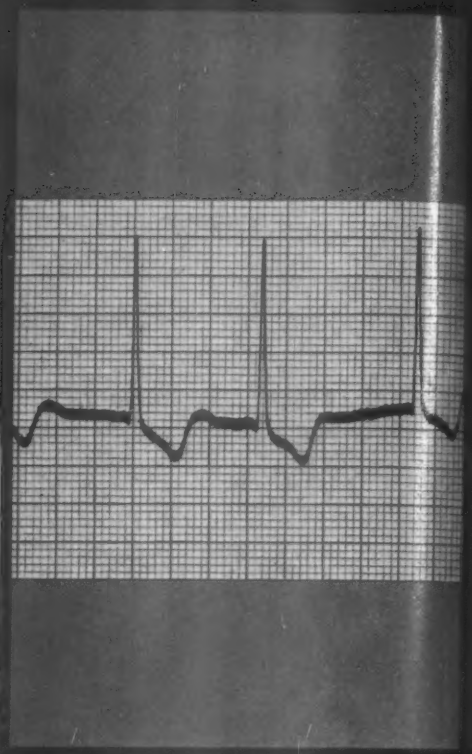
Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

## *before treatment**

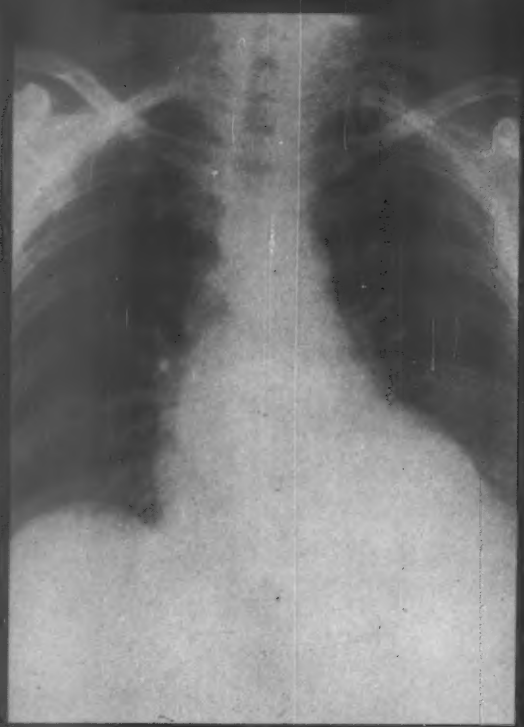


Cardiac enlargement and pulmonary congestion.

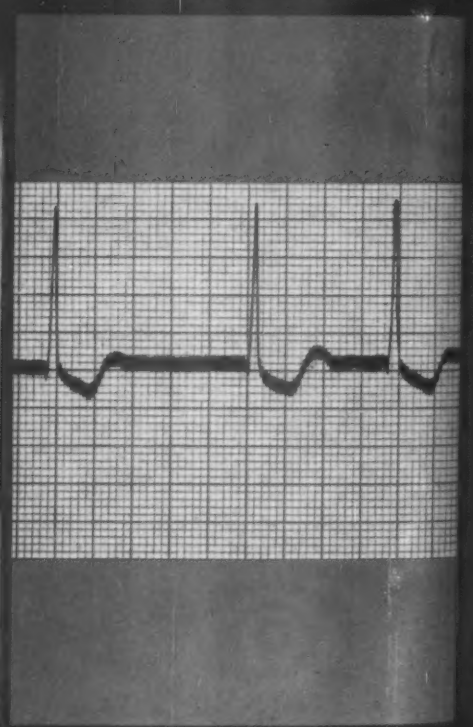


Left ventricular strain and hypertrophy (ST depression in Lead V4).

## *after one month on* HYDROPRES*



Reduction in heart size and clearing of congestion.



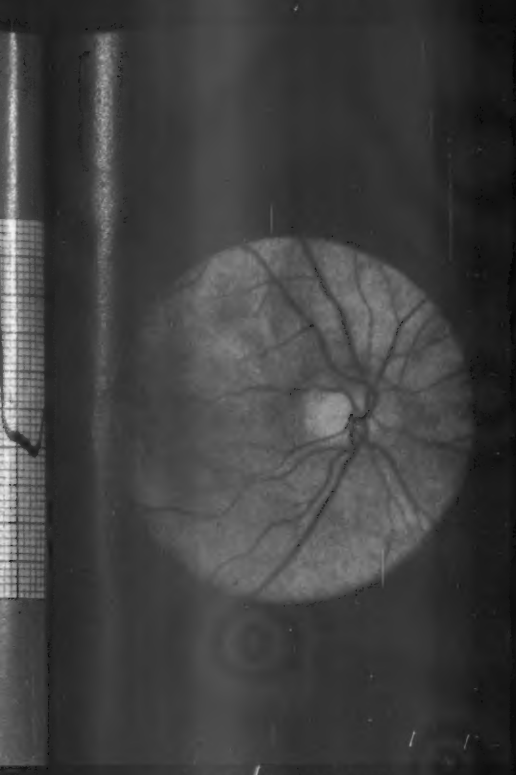
Changes toward normal (less ST depression).

***case report**

**effective by itself in many hypertensives...**
**indicated in all degrees of hypertension**

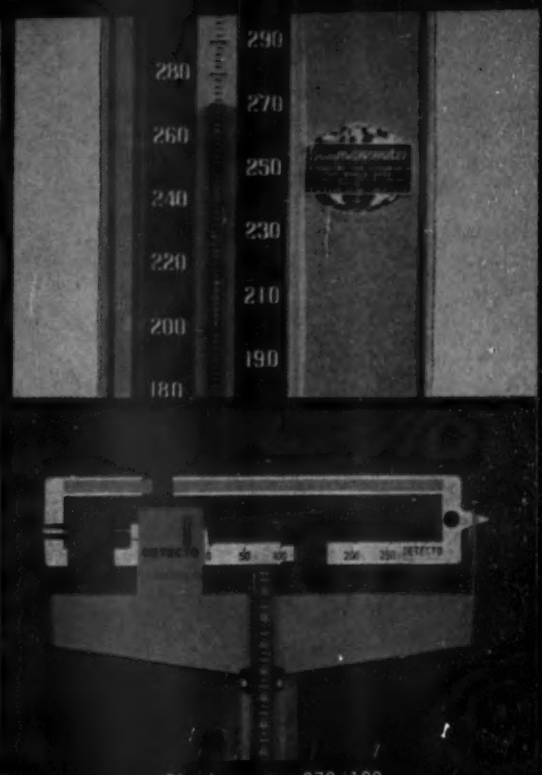
# HYDROPRES®

**HYDRODIURIL®** HYDROCHLOROTHIAZIDE **with RESERPINE**

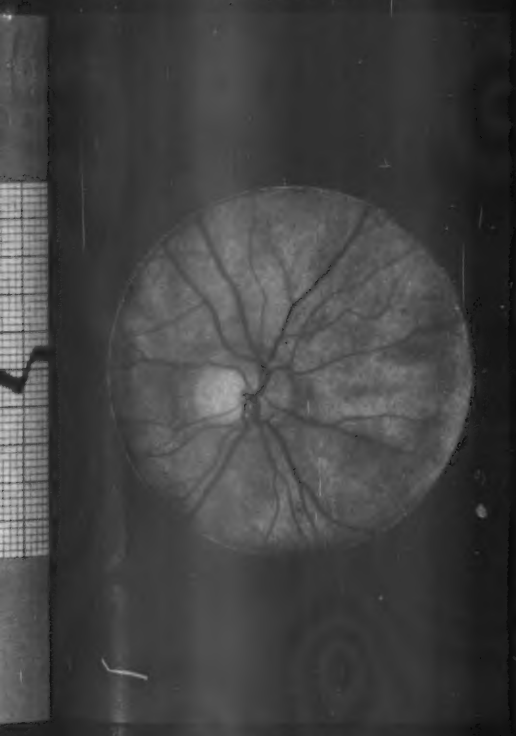


Hypertensive retinopathy with hemorrhages.

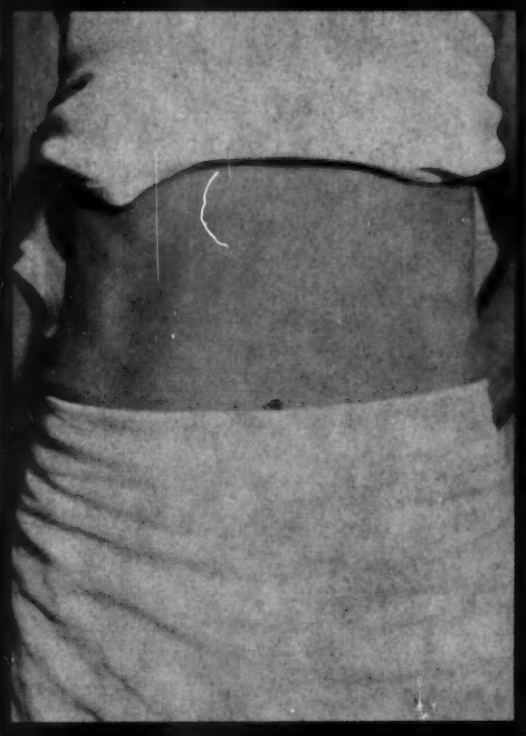
Liver palpable 5 fingerbreadths below costal margin.



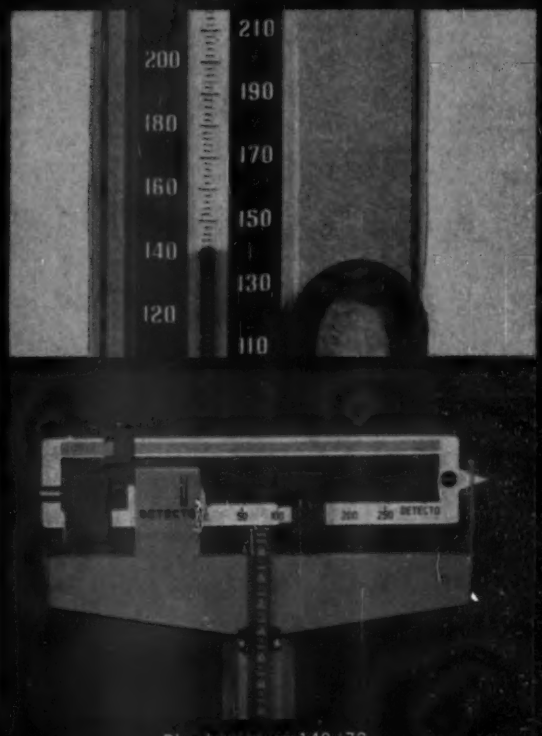

Blood pressure 270/120.
Weight 110½ pounds.



Very little change.



Liver not palpable.




Blood pressure 140/72.
Weight 105 pounds.


# THE *Yorke* CREED

THE PURPOSE OF the Yorke Medical Group is to contribute to the improvement of human health and well being through the publication of medical research and experiences, as controlled by our Physician-Surgeon Editorial Boards. Our code of conduct shall be—

To obtain the most qualified personnel available to serve on our Editorial Staffs.

To select material only on the basis of its scientific merit and value to the profession and such selection shall be the sole and exclusive responsibility of the Physicians and Surgeons who comprise the Editorial Boards.

To limit advertising to ethical pharmaceuticals and reputable medical equipment or services of immediate interest to our subscribers. Advertising must be consistent in standards with the editorial policies of the Journals.

Medical journals present the recorded experiences of the profession and serve as a basis for new researches and life preserving developments.

THE YORKE GROUP
NEW YORK, N. Y.

*THE AMERICAN JOURNAL OF SURGERY*
*THE AMERICAN JOURNAL OF MEDICINE*
*THE AMERICAN JOURNAL OF CLINICAL NUTRITION*
*THE AMERICAN JOURNAL OF CARDIOLOGY*
*MODERN DRUGS*

# FOR ANGINA

Nitroglycerin is the drug of choice for the **ACUTE ATTACK**

# 'CARDILATE'

may well be chosen for **PROLONGED PROPHYLAXIS**

**CLINICAL OPINION**

"... the magnitude of the response to 15 mg. ['Cardilate'] was comparable to that following nitroglycerin.... The comparatively prolonged duration of action of erythrol tetranitrate when given sublingually makes it especially valuable for clinical use."[1]

**CLINICAL OPINION**

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most potent of all prophylactic agents available for the treatment of patients with angina pectoris."[2]

**CLINICAL OPINION**

"Erythrol tetranitrate exhibits an inherent long-acting vasodilating effect. Therefore it is the drug of choice in angina pectoris."[3]

**'CARDILATE'** brand
Erythrol Tetranitrate Sublingual Tablets

**NEW**

5 mg., scored 

15 mg., scored 

Bottles of 100 tablets.

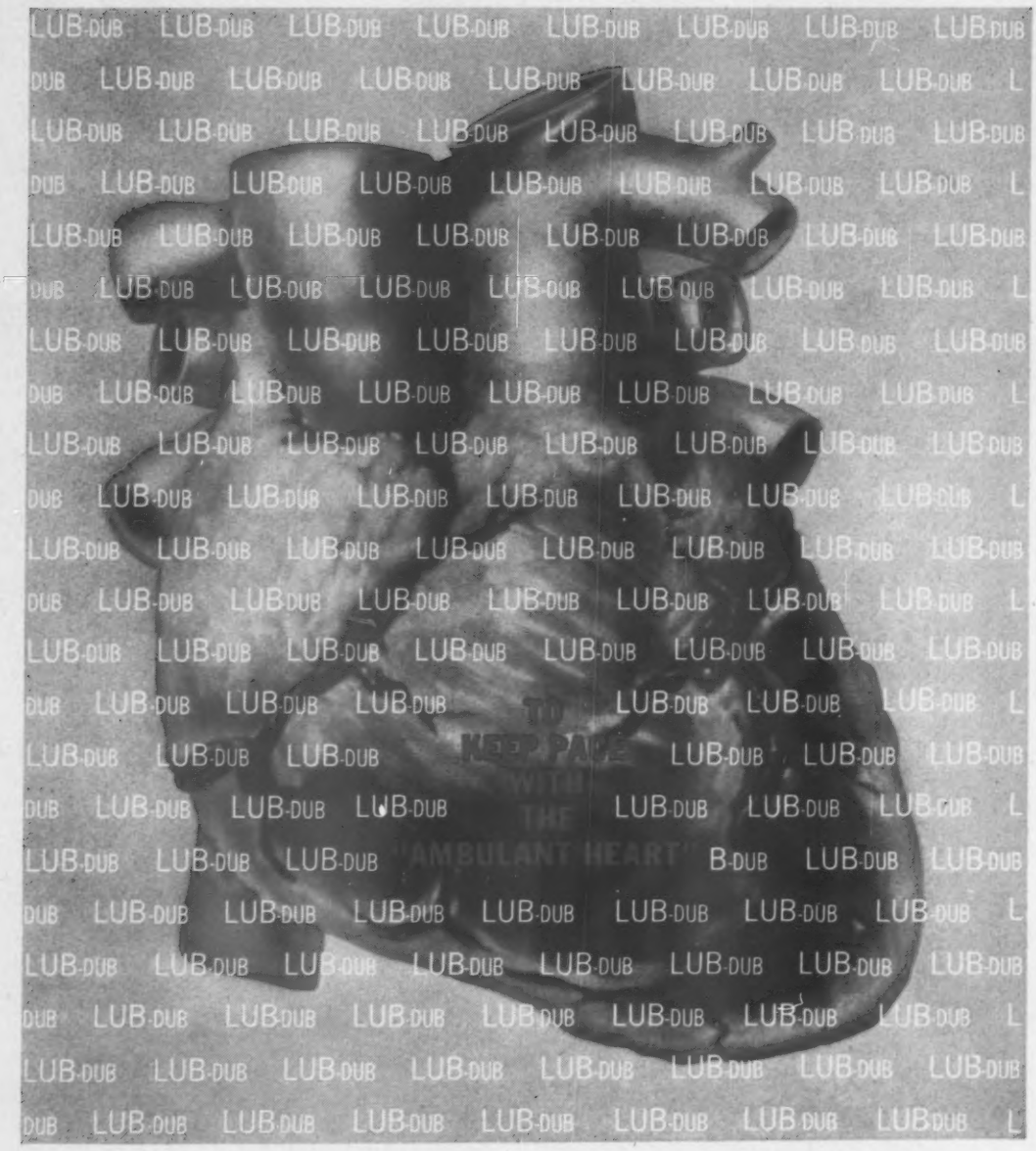
Complete literature available on request.


1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.


**BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York**




# DIAMOX®

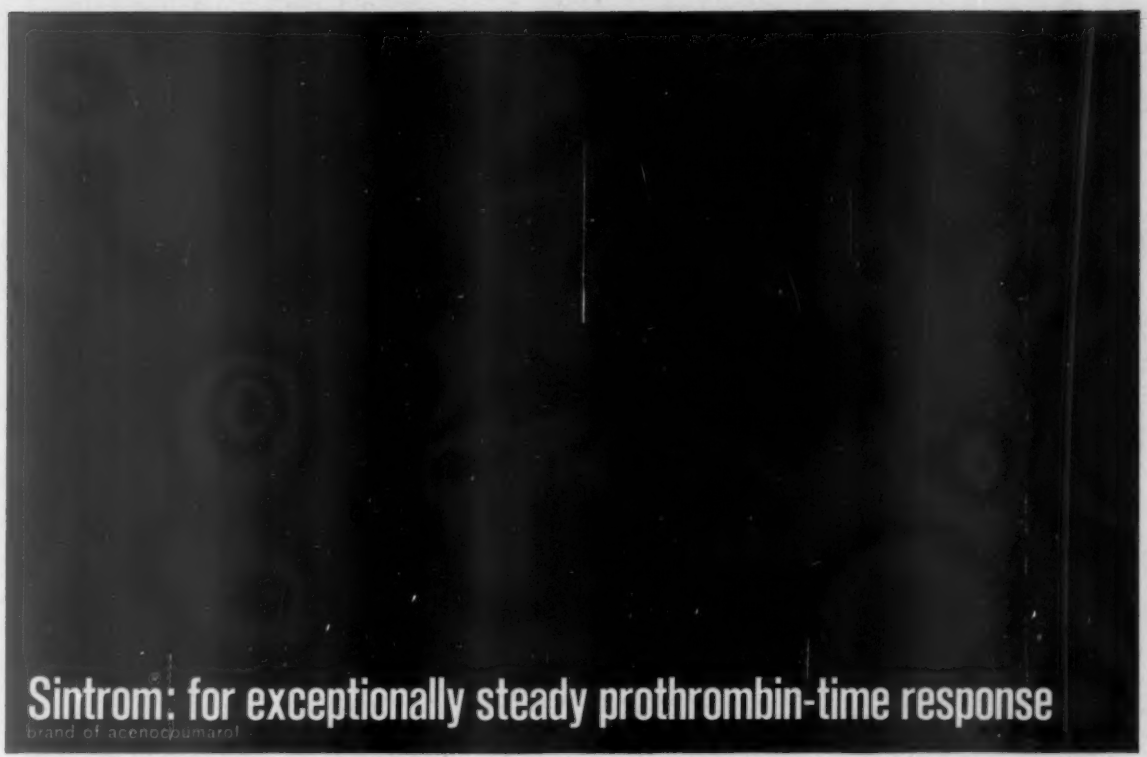
ACETAZOLAMIDE LEDERLE

## *For gentle diuresis*

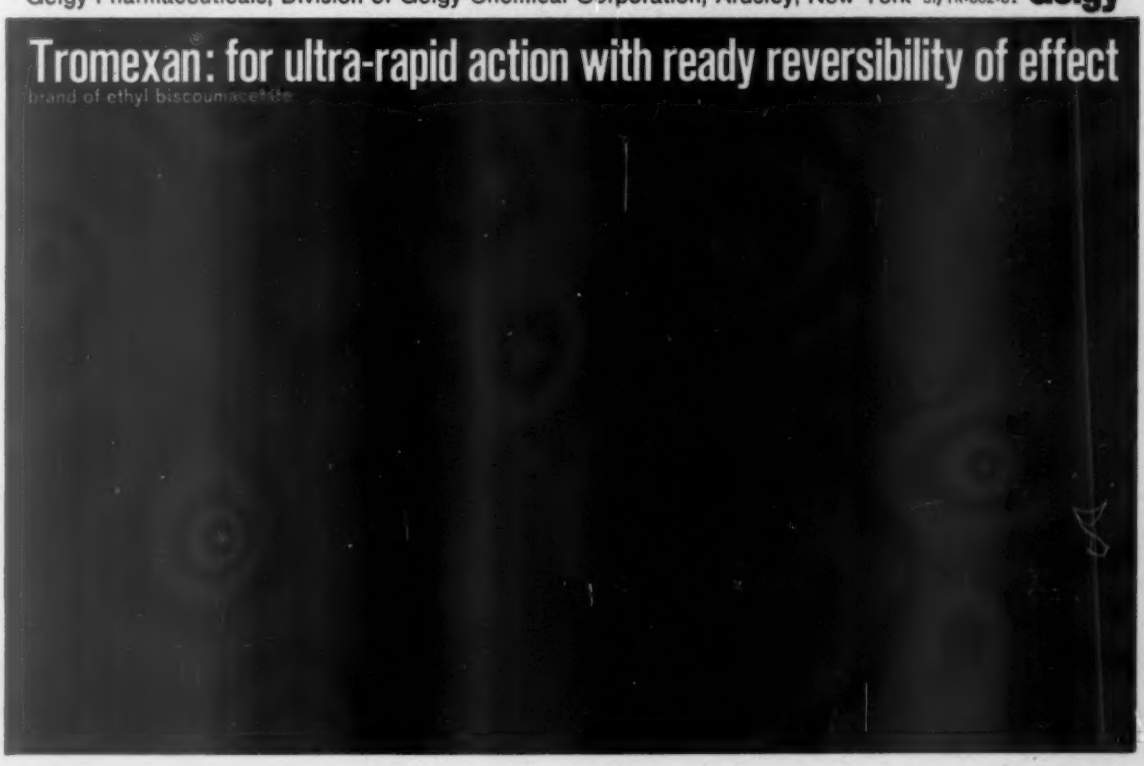
**In mild to moderate decompensation, DIAMOX closely matches diuretic action to diuretic needs. Gentle removal of water is achieved without distorting normal electrolyte ratios. A single morning dose provides comfortable, self-limiting daytime action and nighttime rest. Tablets of 250 mg. Parenteral, vials of 500 mg.**

***Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.***

**LEDERLE LABORATORIES. A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York**




**Two established oral anticoagulants.** In the treatment of thromboembolic disease, both Sintrom and Tromexan reliably bring about hypoprothrombinemic response.
Distinguished by high potency and its ability to maintain a uniform response with a constant single daily dose, Sintrom is particularly suited to long-term therapy. Significantly more rapid and transient in action, Tromexan is well adapted to cases calling for more immediate control of thrombotic tendencies.
Full information regarding dosage, side effects, precautions and contraindications available on request.
**Sintrom®, brand of acenocoumarol, is supplied as double-scored tablets of 4 mg.**
**Tromexan®, brand of ethyl biscoumacetate, is supplied as single-scored tablets of 150 and 300 mg.**
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York SI/TR-662-61 **Geigy**



# IN SHOCK OF MYOCARDIAL INFARCTION

INJECTION

# ARAMINE®

(metaraminol)

"...A strong pressor effect with a myocardial-stimulating action in experimental studies."[1] "...Tens of thousands of intramuscular and subcutaneous injections. ... Not a single instance of tissue injury was observed."[2]

ARAMINE can be administered for pressor effect by any route—subcutaneous, direct intravenous, intramuscular, intravenous infusion. No slough reported **when injected into preferred vein of arm.** Minimal risk of causing arrhythmias.

Onset of action (intravenous): 1 to 2 minutes.

ARAMINE is always ready for immediate use—no dilution needed.

ARAMINE is also valuable in shock accompanying anaphylaxis, brain damage, infectious disease, hemorrhage, surgery, trauma.

**Supplied:** In 1-cc. ampuls and 10-cc. vials (10 mg. metaraminol present as the bitartrate per cc.).

ARAMINE is a trademark of Merck & Co., INC.

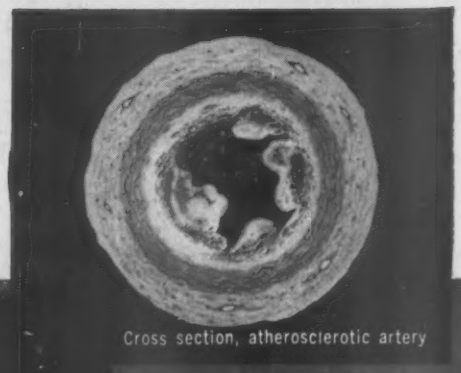
Additional information is available to physicians on request.

1. Seizer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762 (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

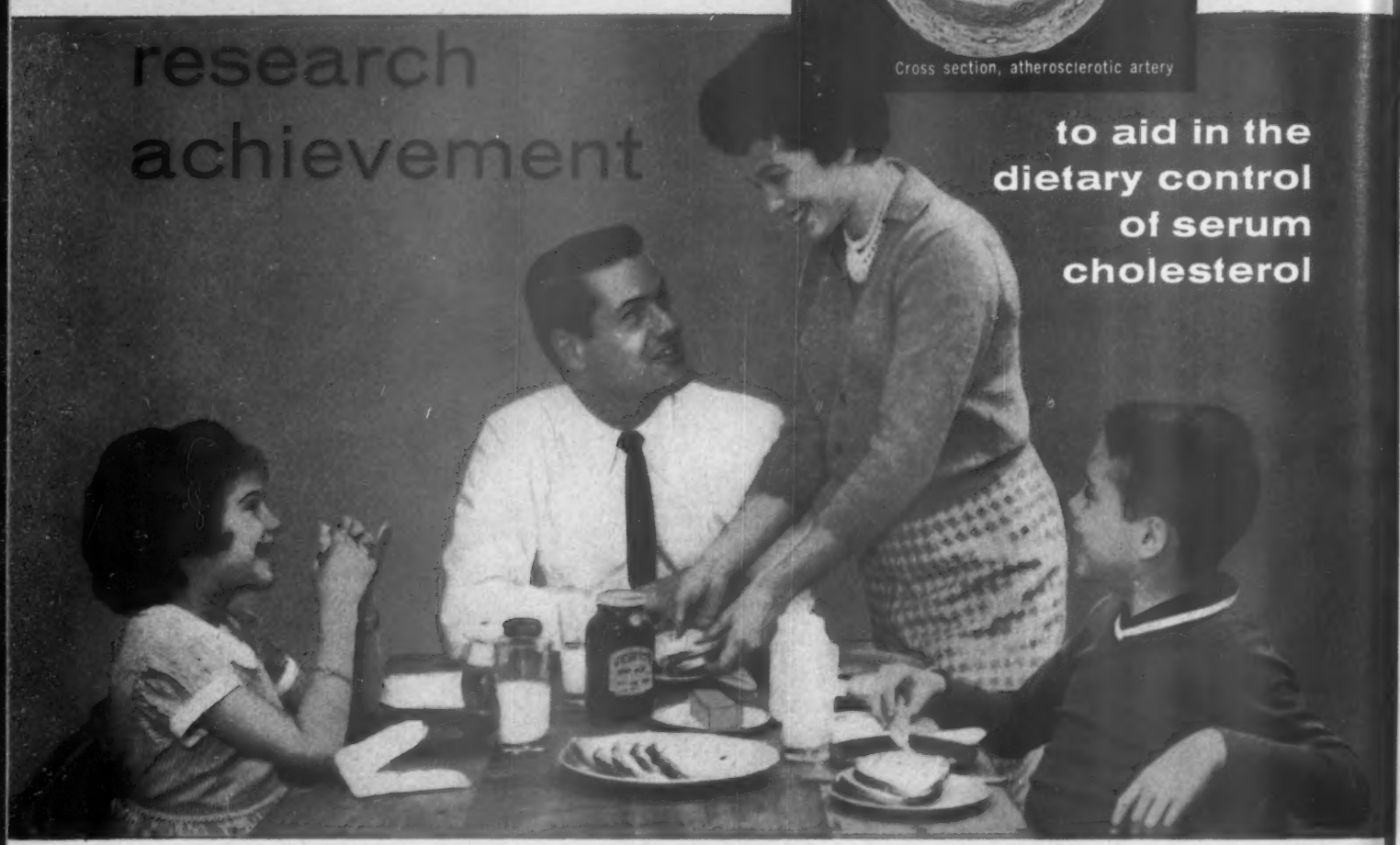
MSD MERCK SHARP & DOHME, Division of Merck & Co., INC., West Point, Pa.

# outstanding nutritional research achievement



Cross section, atherosclerotic artery

**to aid in the dietary control of serum cholesterol**



# MAZOLA®

**MARGARINE**
scientifically formulated with pure liquid non-hydrogenated MAZOLA Corn Oil.

U.S. Pat. No. 2,955,039

MAZOLA Margarine is an economical tablespread and serves as a solid shortening, rich in linoleates and low in saturates—making it an ideal dietary adjunct in the management of serum cholesterol. It contains 2 to 3 times as much natural linoleic acid as any other margarine readily available in grocery stores from coast to coast, and 5 to 8 times as much as butter. It contains no dairy or animal fats, no coconut oil, and no cholesterol.

MAZOLA Margarine is indistinguishable from other quality margarines as to taste, aroma and handling characteristics. Thus, it can be part of the regular diet for the whole family, including the hypercholesterolemic patient. The major ingredient in MAZOLA Margarine—liquid MAZOLA Corn Oil—is NOT hydrogenated, thereby preserving its rich content of linoleates.

The average daily intake, two ounces or 56.8 Gm. (4 tablespoons) of MAZOLA Margarine, supplies

| | |
|---|---|
| Linoleic acid | 12 Gm. |
| Oleic acid | 23 Gm. |
| Saturated fatty acids | 8 Gm. |
| Plant sterols (sitosterols) | 215 mg. |
| Natural tocopherols | 30 mg. |
| Vitamin A | 1870 USP units |
| Vitamin D | 250 USP units |
| Calories | 415 |

Available in the refrigerator sections of grocery stores in the same general price range as other premium quality margarines, in 1-lb. packages (four ¼ lb. sticks).

Send for free booklet:
"Recent Advances in the Dietary Control of Hypercholesterolemia."

**BEST FOODS** • Division of Corn Products Co., NEW YORK 22, N.Y.

# oral aminophylline

# readily tolerated

## by almost every patient

# AMINOPHYLLINE DURA-TAB S.M.®

Oral Sustained Medication* Aminophylline 4½ gr. (.3 Gm.)

## one dose q.12 h. maintains effective uniform blood levels in cardio-pulmonary conditions

Many patients who cannot tolerate ordinary aminophylline tablets can now take **Aminophylline Dura-Tab S.M.** without gastric irritation. The reason: only a fraction of this sustained-action aminophylline contacts the gastric membranes — the balance being absorbed slowly all along the intestinal tract.

**one dose q. 12 h.** (1 to 2 Aminophylline Dura-Tabs) in adults maintains effective blood levels. For children under 10, one-half Dura-Tab q. 8 to 10 h. • Indicated in bronchial asthma, pulmonary emphysema, congestive heart failure, angina pectoris, paroxysmal dyspnea and Cheyne-Stokes respiration.

**Bottles of 30, 100, 250 — cost comparable to ordinary aminophylline tablets.**

*U. S. Patent No. 2,895,881

*Samples* and literature upon request.

**WYNN** PHARMACAL CORPORATION

Lancaster Ave. at 51st Street, Philadelphia 31, Pa.

SEE US at Booth #W-31—AMERICAN MEDICAL ASSN. ANNUAL MEETING

June 25–30—New York City

The American Journal of Cardiology

VOLUME VII JUNE 1961 NUMBER 6

# Clinical Studies

## Pulmonary Edema of High Altitude*

VICTOR ALZAMORA-CASTRO, M.D., F.A.C.C., GUILLERMO GARRIDO-LECCA, M.D., F.A.C.C. *and* GUIDO BATTILANA, M.D.

Lima, Perú

OVER THE YEARS numerous instances of pulmonary edema associated with high altitude have been observed in the people of Perú. In 1897, while going up to an altitude of about 4,000 meters (13,200 feet), a twenty-five year old man died from an "acute pulmonary illness." In 1937, Hurtado[1] described a case of pulmonary edema in an Indian who became acutely ill after returning from sea level to high altitude. In 1945, one of us examined a thirty-nine year old man with a normal cardiovascular system in whom "pulmonary edema" developed after he went to an altitude of 3,500 meters (11,550 feet). In 1949, a twenty-nine year old man known by us to have a normal heart, died from an acute pulmonary illness in Oroya, a city located at an altitude of 3,712 meters (12,249 feet). These observations could hardly be coincidental and a rather unusual pulmonary disease due to high altitude was suspected. In the following years additional cases were observed. In 1952, Lundberg[2] described some cases of acute pulmonary edema in "soroche" (acute mountain sickness). In 1955, Lizarraga[3] and Bardales[4] published some additional observations. In July 1958, a member of the Andean American Expedition succumbed to "fulminant pneumonia" while climbing a very high peak of the Andes. We know of many other casualties due to pulmonary edema of high altitude; therefore, it seems important to give information regarding this particular disease.

### CASE REPORTS

CASE 1. A twenty-five year old white man, born and living at an altitude of 2,750 meters (9,000 feet), went hunting on August 21, 1897 at an altitude of 4,000 meters (13,200 feet). That night he had dyspnea and nonproductive cough. In spite of these symptoms he continued his physical activity. Two days later dyspnea became severe and bloody sputum appeared. He went into syncope and died at that altitude on August 23, 1897.

CASE 2. This was a white man of thirty-nine years, born in Quito which has an altitude of 2,840 meters (9,372 feet). In July 1943, on returning to his farm located at an elevation of 3,400 meters (11,220 feet), he suffered "severe pneumonia." In 1944 he was in excellent condition after a complete medical check-up. In September 1945, he returned to his farm and became severely ill. According to his physician he had "pulmonary edema due to heart disease." He recovered within a week and came to Lima. Here a complete medical examination was unremarkable; blood pressure was 130/80 mm. Hg. The electrocardiograms were within normal limits at rest and following an exercise tolerance test. The teleoroentgenogram of the chest was also normal. Further medical examinations revealed no cardiac abnormality. In November 1945 he went back to his farm and severe "pulmonary edema" returned on the second day.

* From the Departments of Internal Medicine and Cardiology, Hospital Dos de Mayo, University of San Marcos Medical School and British American Hospital, Lima, Perú.

CASE 3. A white man born at 2,750 meters (9,000 feet), later lived in Lima and became an air-force pilot. In 1947 a complete cardiovascular examination disclosed no abnormality. He had often been at high altitudes. On February 2, 1949 at the age of twenty-nine years, he went to Oroya, 3,712 meters (12,249) feet). At this time he had a mild "common cold." A few hours after arrival he had palpitations and dyspnea. The next day severe dyspnea, precordial oppression and cyanosis developed. He was given digitalis and antibiotics. On Febraury 4 the clinical picture worsened. The sputum became bloody and the lungs "made a noise like squeezing papers." He died early on the morning of February 5, 1949.

CASE 4. Born at sea level, this forty-one year old white man had previously been at high altitudes without bad results. On June 19, 1956 he went to Oroya, 3,712 meters (12,249 feet), and soon after arrival had dry cough, headache and palpitations. Hours later he had dyspnea. On June 21 his condition worsened and orthopnea, cyanosis, bloody sputum and intense headache appeared. On June 22 it was decided to transport him to sea level, but he died in the automobile.

CASE 5. A white man, born at sea level in 1919, was under treatment for pulmonary tuberculosis from 1937 until 1947. In 1941 he traveled to a mine located at 3,500 meters (11,550 feet) and a "severe pulmonary infection" obliged him to return to sea level. The respiratory symptoms disappeared as he descended. At sea level he was perfectly healthy. In 1957 he returned to the mine. On the second day pulmonary symptoms appeared and "severe pneumonia" was diagnosed. He was transported to sea level where, as before, the pulmonary symptoms disappeared during the trip.

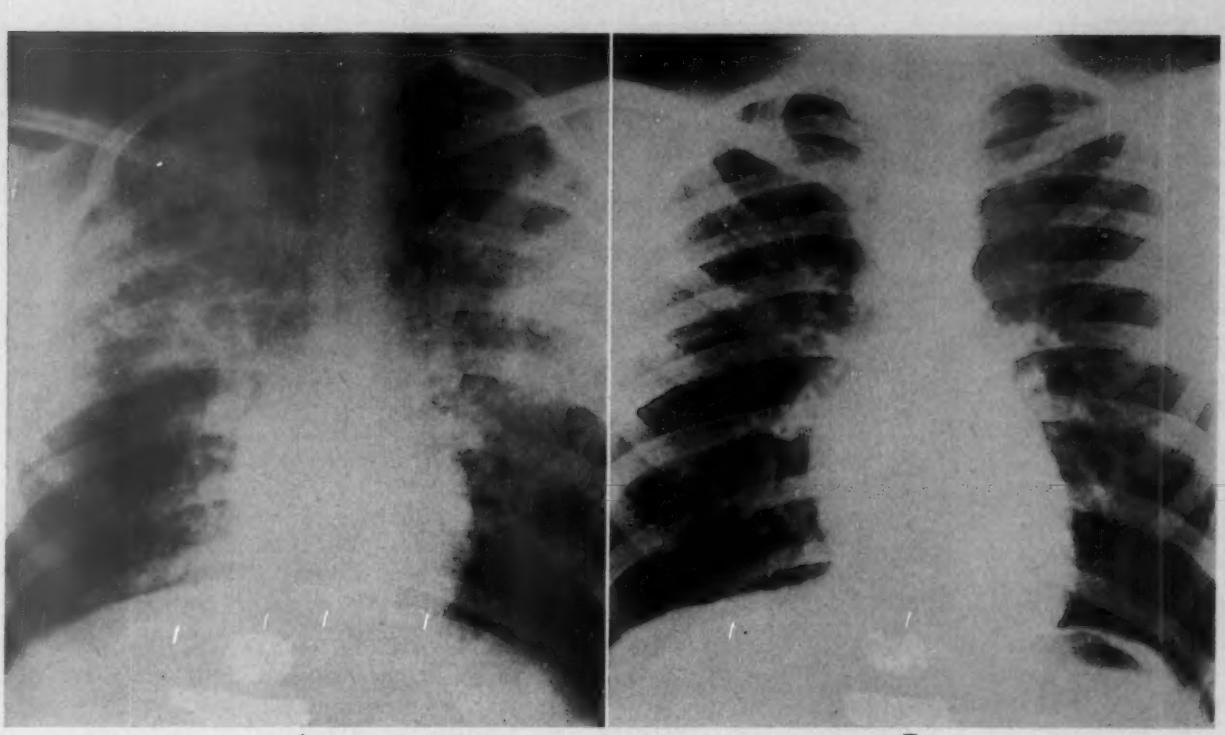
CASE 6. A thirty-two year old Peruvian man, born in a city with elevation of 2,370 meters (7,821 feet), went to Huancayo in 1944, elevation 3,266 meters (10,777 feet). The trip was uneventful. In July 1950 he went to Cuzco, 3,410 meters (11,253 feet). On arrival he noticed palpitations and dyspnea and could not sleep. The next day dyspnea became severe. He went to a hospital and oxygen was administered; the dyspnea and the "noise" in the chest improved. On the fourth day, when oxygen was temporarily discontinued, syncope occurred. He was hospitalized for eight days, during which time there was no fever or other sign of infection. He left the hospital and for three days led an active life in the altitude without marked symptoms. On July 31, 1950 a complete cardiovascular examination in Lima was within normal limits, including electrocardiograms and cardiac fluoroscopy.

CASE 7. A four year old Peruvian girl, born at sea level, went in January 1953 to Cerro de Pasco, 4,359 meters (14,380 feet). She complained of severe dyspnea and cyanosis soon after arrival. She had no fever. According to her parents she was very sick and heart disease was suspected. Subsequent examination of the girl did not reveal heart disease.

CASE 8. A fourteen year old Japanese boy, born at sea level, attended school in a city located at 3,266 meters (10,777 feet). In 1954 he was sent down to Lima for a two week vacation. A few hours after returning to his school he had a severe attack of dyspnea and dry cough followed by orthopnea and "pink sputum." He was treated with digitalis and 500 cc. of blood was withdrawn without much improvement; pulse rate was 150 per minute and blood pressure 90/60 mm. Hg. On the second day his condition became worse. Dyspnea was intense and for several minutes the patient lost consciousness. He was brought down to the coast by automobile. During the trip, at an altitude of 4,853 meters (16,000 feet), the patient lost consciousness again and was extremely ill. As he began to descend his condition improved and two hours later, between 2,000 and 1,000 meters (6,600 and 3,300 feet) above sea level, the patient showed marked improvement and he complained only of headache. On arrival in Lima examination showed rales throughout both lung fields as well as slight cyanosis but no evidence of heart disease. There was no fever. The electrocardiograms and routine laboratory examinations were within normal limits. On the second day all signs disappeared and the patient had no more complaints.

CASES 9 and 10. These two patients were school boys aged fourteen who had been born and had lived at high altitudes of about 3,300 meters (10,800 feet). They came down to sea level for a period of ten to seventeen days. On returning to high altitude they soon had cough, accompanied by cyanosis and orthopnea. Both were treated with digitalis and oxygen without improvement so they had to return to sea level. They recovered completely as soon as they arrived at Lima. Both were examined and no evidence of heart disease was found. Their electrocardiograms taken soon after arrival were within normal limits. The x-ray films of the chest showed mottled areas and congestion in both lung fields; this disappeared four days later (Fig. 1). The routine laboratory tests were within normal limits and no fever was recorded in either patient.

CASE 11. A fifteen year old white boy, born in a mining camp, 3,300 meters (10,800 feet) above sea level, always lived there except for yearly trips to sea level for periods of two weeks to three months. When he was seven years old, after returning to the highland, he had severe "soroche" (mountain sickness). On July 28, 1955 he came to Lima and went back to the higher altitude on August 15. The next morning he had dyspnea, cough and raised a yellowish sputum; headache and nausea were



A B

FIG. 1. Case 9. A, x-ray film of the chest taken at sea level soon after arrival (August 14, 1955). B, four days after (August 18). The only treatment was bed rest.

present. In the afternoon dyspnea was severe and cyanosis was observed. He had no fever. Pulse rate was 145 per minute and the blood pressure 90/70 mm. Hg. A physician diagnosed acute heart failure. Ouabain and oxygen were administered and then 400 cc. of blood was withdrawn from the arm. With this treatment the patient said "within thirty minutes I was breathing better but my chest was full of phlegm and the sputum was abundant." On the next day his temperature was 37° C. (99° F.), but his condition was definitely improved. He received oxygen for two days and then was brought by airplane to Lima, where examination disclosed wet rales in both lung bases. He had slight cough and salmon-colored sputum but no dyspnea. Next day the x-ray films of the chest, the electrocardiograms and routine laboratory analysis were within normal limits and the sedimentation rate was 26 mm.

CASE 12. A white man born at sea level had been living for many years in Cerro de Pasco, 4,359 meters (14,380 feet). He had made several trips to Lima, at sea level, and never felt any unusual symptoms on returning to the high altitude. On May 18, 1956, when he was thirty-six years old, he returned to Cerro de Pasco after a short visit to Lima. The first morning he felt nothing unusual but in the afternoon after a heavy meal including four or five bottles of beer, dyspnea appeared. After intercourse severe pulmonary edema developed and he had to be hospitalized. He remained at the hospital for three days during which time oxygen was given. While he suffered from the pulmonary edema the blood pressure rose to 190/100 mm. Hg. The blood count and sedimentation rate were within normal limits and there was no fever. He left the hospital and came down to Lima. He was examined on June 2 and his cardiovascular system was found to be within normal limits.

CASE 13. A five year old girl, born of North American parents in La Paz, Bolivia, elevation 3,642 meters (12,018), had lived in Lima since the age of one and a half years. In 1953, at the age of two years, she was taken to Morococha, 4,540 meters (14,982 feet), and nothing particularly abnormal was noticed. Six months later she was taken to Lima, at sea level, and then back to Morococha. This time she was short of breath, pale and cyanotic. This condition lasted four days and then disappeared. Until 1956 every time she returned from Lima to Morococha the same symptoms were observed. On November 28, 1956, five hours after arriving in Morococha, she had severe dyspnea, vomiting and bloody sputum; pulse rate rose to 170 per minute and cyanosis was marked. Oxygen was administered without any definite improvement. During the trip to Lima she gradually recovered. She slept quietly in Chosica, 800 meters (2,640 feet) above sea level. A complete examination disclosed a normal cardiovascular system.

CASE 14. A white man born at sea level was fifteen years old when he went to Cerro de Pasco,

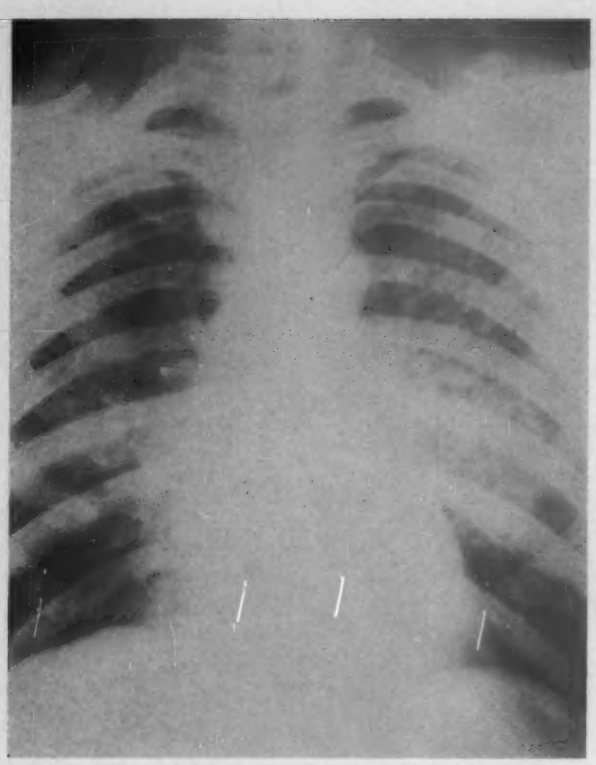


FIG. 2. Case 22. X-ray film of the chest. Pulmonary edema of high altitude is observed in both lungs.

4,359 meters (14,384 feet). After the second day he was dyspneic and during the third night had acute pulmonary edema. Instead of taking him back to Lima, a trip which makes it necessary to pass through higher places, his father, apparently familiar with this complaint, took his son to Huanuco, 1,912 meters (6,309 feet). When he reached this place his symptoms disappeared. In the last twenty years this man has gone monthly to a mine located at 4,500 meters (14,850 feet) and never had any symptoms. He was sent to us because of the history of acute pulmonary edema. His cardiovascular system proved to be within normal limits.

CASE 15. A forty-six year old Peruvian man, born at sea level, made frequent trips to Cerro de Pasco, 4,359 meters (14,384 feet) and to Morococha, 4,540 meters (14,982 feet). He never felt the effects of the altitude until November 1959 when he went to Cerro de Pasco. He complained of a mild common cold with a "dripping nose" but felt well. On the fourth day after arrival he performed very active work and while climbing to a second floor became ill and had severe dyspnea for three hours. He recovered spontaneously. A few days later examination showed a normal cardiovascular system. He went back to the higher altitude and no symptoms were observed.

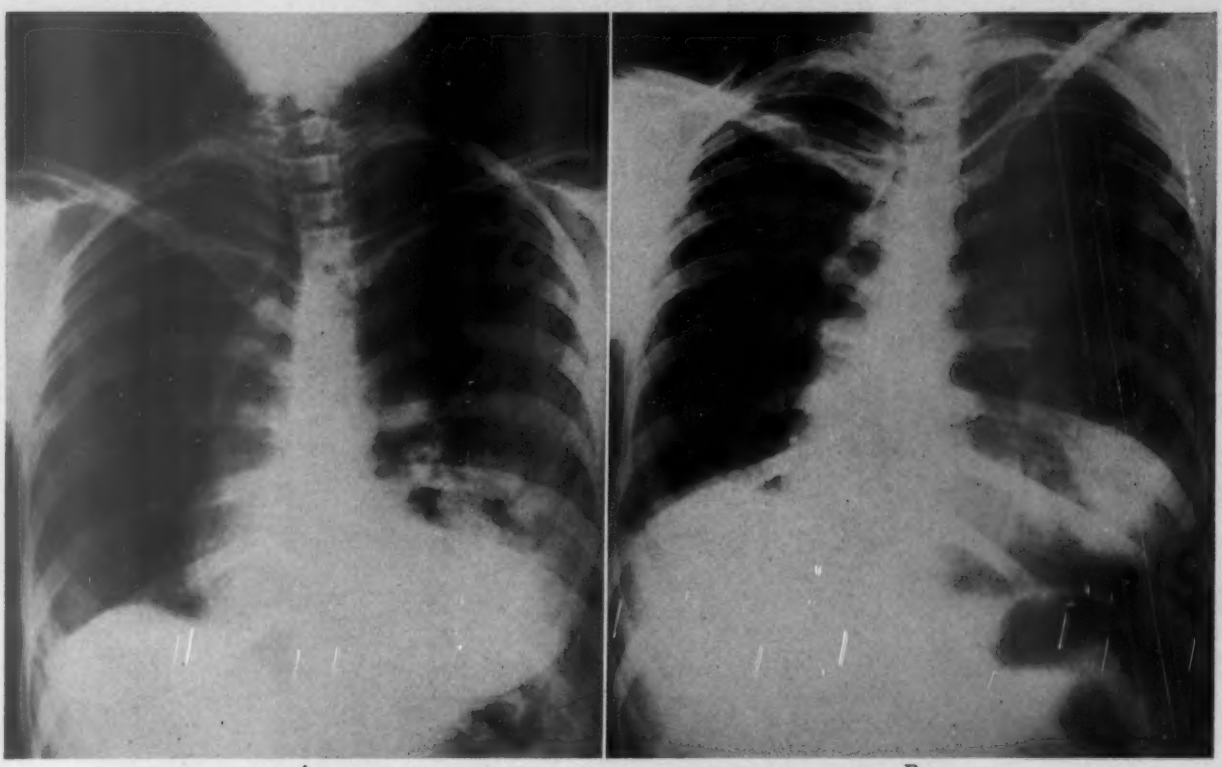
CASE 16. A thirty-six year old Peruvian man born in Huancayo, 3,266 meters (10,777 feet), always lived at this altitude. In June 1952 he went to Morococha, 4,540 meters (14,982 feet), and three hours later became dyspneic and "his chest was full of water." Knowing about this acute soroche he rented a car and went to Huancayo where he had lived for years. In Huancayo his condition was still not good so he went even lower, to Huánuco, 1,912 meters (6,300 feet). Three days later he returned to Huancayo. The trip was uneventful. In July 1952 his heart was noted to be within normal limits.

CASES 17, 18 and 19. These are three Peruvian men, aged twenty, twenty-six and thirty-six years. Two were born at a high altitude and one at sea level. All have often been in high altitudes. On one of the trips to a city located at 4,359 meters (14,384 feet), pulmonary edema developed soon after their arrival. Two of these men have returned to the high altitude without discomfort; one has never been back. Medical examinations did not reveal any abnormalities and their cardiovascular systems were found to be within normal limits.

CASE 20. A fifteen year old Peruvian boy, born at a high altitude, spent two weeks at sea level and returned to the highlands. A few hours after arriving at 3,255 meters (10,741 feet) a cough developed and he was orthopneic. He was treated successfully with oxygen and digitalis. Medical examination did not reveal heart disease.

CASE 21. A thirteen year old Peruvian boy was born and lived at 3,266 meters (10,777 feet). He came to Lima for a three month vacation for seven consecutive years. The last time he felt somewhat tired and had a cough four hours after arrival. Six hours later pulmonary edema developed and he was treated with oxygen and digitalis. Because there was no improvement, 300 cc. of blood was removed and he was brought down to Lima. The patient was cyanotic and markedly orthopneic. He coughed and raised a blood-tinged sputum. The heart rate was 150 per minute. The heart sounds were normal. Both lung fields were full of coarse wet rales. Laboratory findings on admission revealed hemoglobin 19.14 gm. per cent; red blood cell count was 7,100,000 and white blood cell count was 16,600 with a normal differential count. Urinalysis revealed a trace of albumen and granular casts. On arrival the venous pressure was 120 mm. water. The x-ray film of the chest showed marked pulmonary edema. The electrocardiograms were within normal limits. On discharge eight days later, hemoglobin was 14.04 gm. and the red blood count was 5,200,000. After two months at sea level he returned to the high altitude without having any symptoms. He has been seen four times and has not had further trouble on returning to the same place.

CASE 22. This forty year old North American priest suffered from pneumonia on four different occasions during a period of ten years, the last attack occurring five years before his trip to Perú.



A B

FIG. 3. Case 25. X-ray films of the chest. A, pulmonary edema of high altitude is predominant in the left lung. B, at sea level two days later. Both lung fields show a more normal appearance. The patient was treated only with oxygen and 400,000 units of penicillin.

After a few days in Lima he went to Cuzco, 3,410 meters (11,253 feet), where he was somewhat tired and was unable to sleep because of mild shortness of breath. The next day he went on a tour and felt worse. That night dyspnea became severe and he felt his chest "full of phlegm." He coughed, his head ached and he felt very restless. He was taken to the hospital where he had temperature of 38° C. (100° F.), a pulse rate of 130 per minute and blood pressure of 160/100 mm. Hg. He was treated with digitalis and 600 cc. of blood were withdrawn from a vein in the arm. When he did not improve, he was taken to sea level by plane. On arrival at sea level he still had severe dyspnea and cyanosis. Heart rate was 110 per minute, blood pressure 110/90 mm. Hg and venous pressure was 95 mm. of water. Moist rales were heard in both lungs. Temperature was 38° C. (100° F.). The x-ray film of the chest showed passive congestion in both lungs (Fig. 2). The electrocardiograms revealed RS-T and T wave changes mainly due to digitalis. The patient's condition improved next day. On the third day the x-ray film showed slight congestion in the left lung. The electrocardiogram was unchanged. No fever was recorded. The patient left the hospital in good condition.

CASE 23. This is a thirteen year old Peruvian girl born at sea level. In 1957 she made her first trip to Cerro de Pasco, 4,359 meters (14,384 feet). Soon after arriving she was short of breath. Hours later dyspnea became intense and she was hospitalized and treated with oxygen. She improved rapidly and after leaving the hospital continued living in Cerro de Pasco. A year later she came down to Lima and after a few days went back to Cerro de Pasco. This time she had severe pulmonary edema soon after arrival. The x-ray examination showed abnormal signs, mostly in the right lung. She recovered from this episode and came down to Lima for a medical examination. Her heart was within normal limits. Since this time she has been twice at sea level and has made two uneventful trips to Cerro de Pasco.

CASE 24. This was a forty-three year old man born in England. He had been several times at high altitudes without symptoms. He went to Quito, Ecuador, 2,830 meters (9,339 feet), and after arriving had a headache and general malaise. That night he could not sleep because of a dry cough and mild dyspnea. The next day he went to the hospital and reported "I had no fever but could hear the rales in my chest." He spent two days in an oxygen tent. X-ray examination in Quito showed abnormalities due to healed pulmonary tuberculosis and "passive congestion in both lungs." In Lima the heart was noted to be within normal limits and

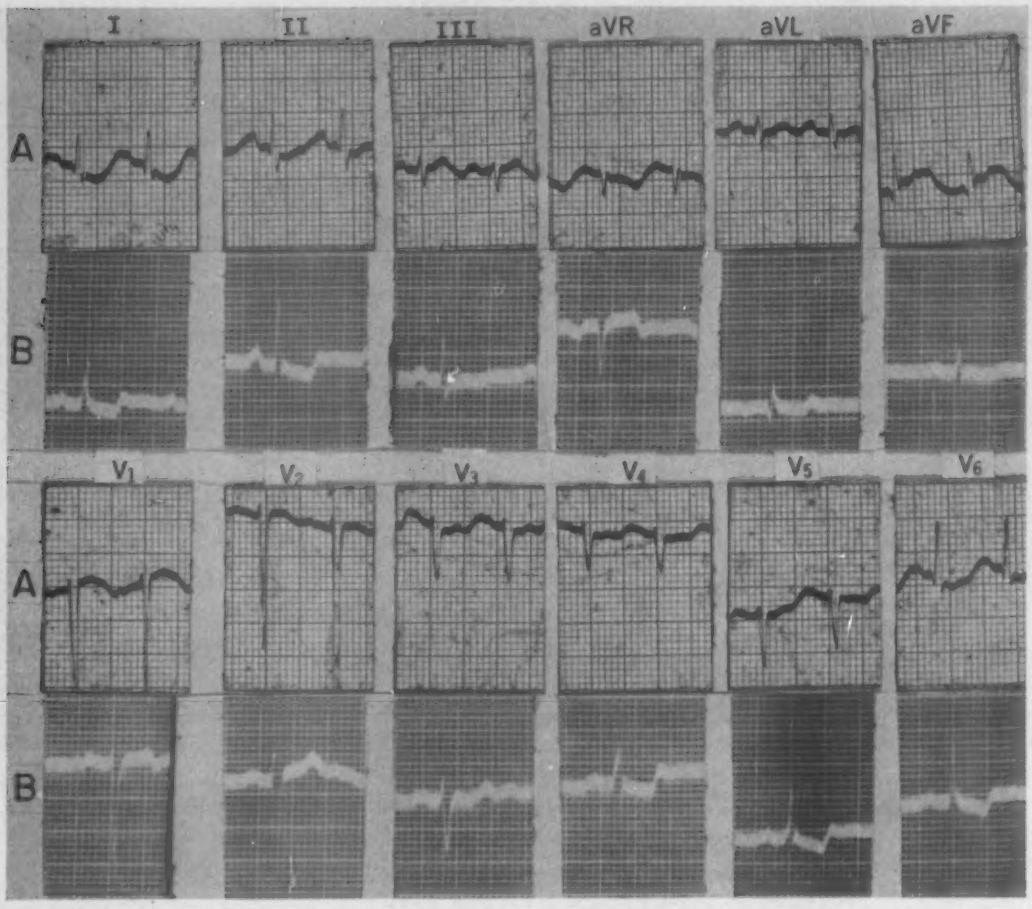



FIG. 4. Case 25. Electrocardiograms. A, tracing on November 10, 1956 at high altitude during pulmonary edema shows sinus tachycardia and changes in the RS-T segments and the T waves, in part due to digitalis. A marked rotation of the heart position is observed. B, on November 13, 1956 at sea level the tracing shows residual changes in RS-T segments, presumably related to digitalis. (PP-139.)

only the old tuberculous lesions were present in the x-ray film of the chest.

CASE 25. This was a thirty-six year old American airline hostess who came to Perú for vacation. She went to Cuzco, 3,410 meters (11,253 feet), by airplane. On arrival she felt short of breath, tired and was unable to sleep that night because of a dry cough. She was able to get up the second day but the next night she became very ill and had severe dyspnea, orthopnea, cough and bloody sputum. She commented "something was rattling in my lungs." Treated with oxygen and digitalis without much result, she was taken by plane to Lima. On arrival she felt ill, had dry cough and cyanosis. Wet rales could be heard in both lungs but were most marked on the left side. The pulse rate was 130 and blood pressure 130/70 mm. Hg. The x-ray film of the chest showed "passive congestion more marked in the left lung." Two days later the x-ray films were nearly within normal limits (Fig. 3). Venous pressure was 120 mm. of water. Blood and urine studies showed no abnormalities. The electrocardiograms taken at the higher altitude showed marked rotation of the electrical axis and changes in the RS-T segments and T waves, whereas those taken at sea level showed only changes of the digitalis type in the RS-T segments (Fig. 4). It is interesting to note that this patient had a temperature of 101° F. on the day of admission and that the temperature was within normal limits the second day. She was treated only with oxygen and 400,000 units of penicillin. The patient was discharged after six days in the hospital.

CASE 26. A fifty-three year old North American white male tourist arrived at La Paz, Boliva, 3,643 meters (12,021 feet). He had a mild infection of the upper respiratory tract. Soon after arrival he had headache, malaise, dry cough and slight dyspnea on exertion. The next day the cough was severe, blood appeared in the sputum and dyspnea increased. A doctor diagnosed pulmonary edema. Digitalis and oxygen were administered but the symptoms did not disappear. The patient was brought on a direct flight from La Paz to Lima. During the trip

he improved and on examination the patient was in no distress. The pulse was 90 and regular, blood pressure 120/80 mm. Hg, heart sounds were normal and there were no murmurs. Temperature was 378° C. (100° F.). Moist rales were heard mostly in the lung bases. Results of routine laboratory analysis were within normal limits. The x-ray film of the chest showed signs of pulmonary congestion and edema in both lung fields, especially on the left (Fig. 5). The patient slept all night; he refused to stay and left the hospital early in the morning after fourteen hours.

CASE 27. This eight year old North American girl had been in Perú for the last three years at a mining camp 4,000 meters (13,200 feet) above sea level. After a five day trip to sea level she returned to the highlands. That night she had a nonproductive cough, dyspnea and orthopnea. Her local doctor gave her digitalis and oxygen. She improved for about eight hours. She was then taken down by automobile to sea level for about five hours. Physical examination showed cyanosis of her nails and lips, some dehydration of the mucous membranes, dyspnea and orthopnea. Both lung fields were full of coarse wet rales. The heart rate was 97 per minute; a grade 2 pulmonic systolic murmur could be heard. No other abnormalities could be detected. X-ray examination on admission showed marked passive congestion of both lungs, mostly on the left (Fig. 6). The electrocardiogram was normal.

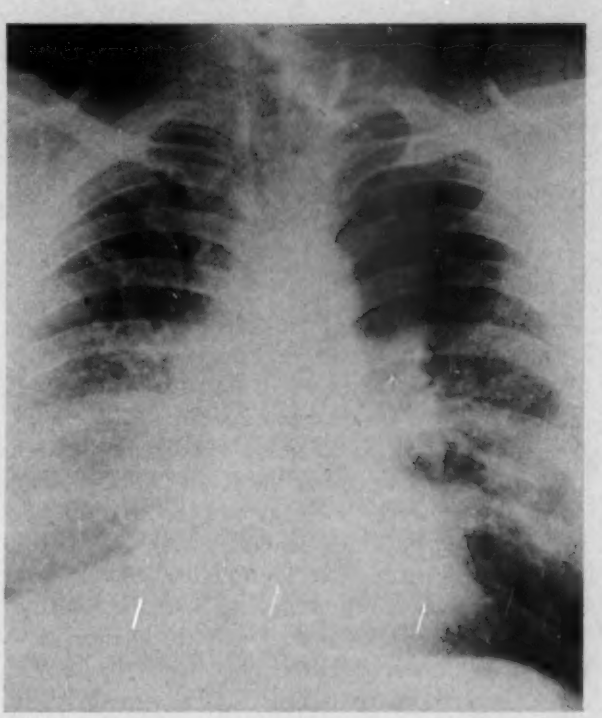
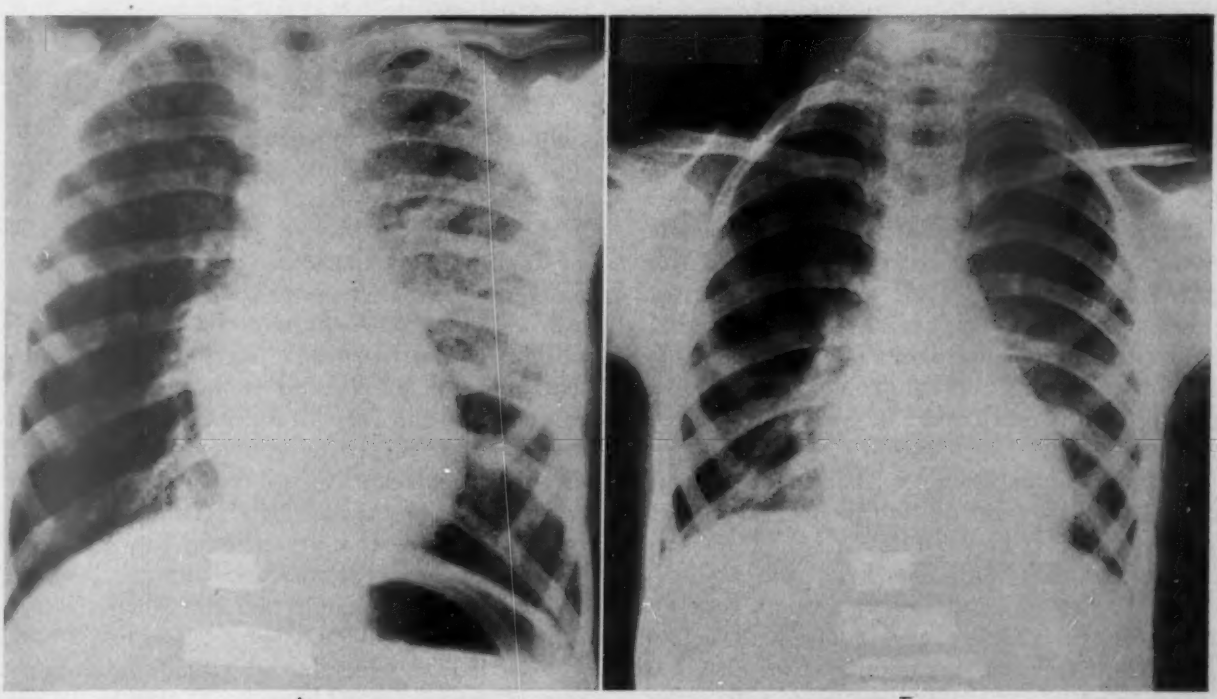


FIG. 5. Case 26. X-ray film of the chest taken at sea level soon after arrival.

The treatment in the hospital consisted only of bed rest and oxygen for six hours on the night of admission. Her condition improved rapidly and on the third day she felt well. The x-ray film of the chest



A B

FIG. 6. Case 27. X-ray films of the chest. A, taken at sea level soon after arrival. Abnormalities are observed mostly in the left lung. B, two days later both lung fields appear normal. The only treatment was bed rest and oxygen for six hours the night of admission.

showed definite improvement (Fig. 6). She was discharged and two weeks later returned to the high altitude. Since then she has been seen twice at sea level. She shows no signs of cardiovascular disease.

## Comments

### CLINICAL FEATURES

Twenty-seven cases of pulmonary edema of high altitude are reported. Most of the patients were men; the youngest was a girl four years of age and the oldest a man of fifty-three years. The majority of the patients were born at high altitudes, about 3,000 meters (9,900 feet); only a few were born at sea level. Of the twenty-seven patients, nineteen were Peruvians, white or mestizo; five were North American; one Equadorian, one Japanese and one English.

In some cases pulmonary edema of high altitude was observed when the first trip to the altitude was made (Cases 7, 23 and 26); in most it occurred in persons who previously had been at high altitudes and who on these trips, felt well or had mild symptoms of acute mountain sickness such as palpitation, headache and insomnia (Cases 3, 11, 15, 17, 18, 19 and 24). Pulmonary edema was often observed in some subjects returning to high altitudes after a short visit to places located at sea level. Pulmonary edema occurred in fourteen and fifteen year old school children who returned to a city located at 3,266 meters (10,777 feet) after a ten to fifteen day visit to Lima (Cases 9, 10 and 20). In some people, pulmonary edema occurred more than once (Cases 2 and 5). A five year old girl had marked symptoms after returning to high altitude; in the last trip she suffered from pulmonary edema (Case 13). In contrast, pulmonary edema was occasionally observed on a first trip and never again (Cases 14 and 27). In some subjects the syndrome was observed during only one of several trips to the highlands (Cases 15, 17, 18 and 21).

There is some evidence that acute respiratory infections were an aggravating or predisposing factor (Cases 3, 15, 22 and 25). It is interesting that pulmonary edema was observed in two subjects with pulmonary tuberculosis (Cases 5 and 24), and in one with several previous attacks of pneumonia (Case 22). In Cases 15 and 26, the oldest patients in our series, pulmonary edema developed simultaneously with a respiratory infection.

In only one instance did pulmonary edema appear the fourth day after arrival (Case 15). In most patients pulmonary edema began the first or the second day with mild dyspnea, headache, palpitation, nausea and nonproductive cough shortly after arrival at high altitudes. Insomnia was often observed. In many cases the premonitory symptoms appeared hours later or the first night. In some the clinical picture began after physical effort, excitation or heavy meal (Cases 12 and 15).

In some patients dyspnea disappeared spontaneously after one or two hours (Case 15). In most cases symptoms were progressive and the condition of the patient gradually became critical. In severe cases the clinical picture resembled cardiac asthma or acute left ventricular failure: dyspnea was intense, pulmonary rales were heard at a distance. The patients were anxious, pale or cyanotic, the skin wet and in many subjects for the first hours the sputum was abundant and bloody, later becoming salmon-colored. Tachycardia was nearly always present. The blood pressure was normal or low, but occasionaly rose during pulmonary edema (Cases 12 and 22). In the three cases in which it was measured the venous pressure was within normal limits (Cases 21, 22 and 25). Some patients complained of precordial oppression, headache, nausea or vomiting. Syncope was observed in three subjects (Cases 1, 6 and 8). Three patients died from this type of pulmonary edema (Cases 1, 3 and 4).

The x-ray films of the chest taken during pulmonary edema showed diffuse mottled areas in both lungs. In four cases the signs of edema were more marked in one lung (Cases 23, 25, 26 and 27). Similar observations have been made by Bardales.[4] When oxygen was administered or when the patient was transported to lower altitudes, the x-ray films of the chest became normal within two to five days. In some subjects already at sea level, abnormal x-ray films of the chest and rales in the lungs were present even though the patients felt very well. The electrocardiograms taken during pulmonary edema showed sinus tachycardia. In some cases moderate changes in the T waves and RS-T segments were observed. In one instance a striking variation in the electrical position of the heart was evident (Fig. 4, Case 25).

The lowest altitude at which pulmonary edema was observed was 2,830 meters (9,339 feet). As a rule, the higher the altitude, the more severe the clinical manifestations. One subject (Case 16) living many years at an alti-

tude over 3,000 meters (9,900 feet) had pulmonary edema when he traveled to a higher place, 4,540 meters (14,980 feet).

If the patient is treated and remains at the high altitude he may recover within a few hours or a few days. It is surprising to note that he may continue living at high altitudes without discomfort afterwards, even doing very active work (Cases 6, 15 and 23). If the patient is transferred by airplane to lower altitudes, recovery is often rapid and dramatic. In the central part of Perú an automobile trip from nearly 5,000 meters (16,500 feet) to sea level takes two to three hours. When patients are transported by automobile they usually feel better in Matucana, elevation 2,375 meters (7,837 feet), and improvement is often evident and symptoms nearly disappear in Chosica, a city elevated 800 meters (2,640 feet), near Lima.

Patients have been treated with digitalis or ouabain, and some have been bled up to half a liter or more. There is no evidence of the benefit of such procedures. Some have been treated successfully with only oxygen. This seems the treatment of choice because the majority of patients improved when they were transported to lower places. Because of fever or because a pulmonary infection was diagnosed, some were also treated with antibiotics. In our series all patients except three were examined and all were found to have a normal heart. None of the patients suffered from Monge's disease or chronic mountain sickness.

## PATHOGENESIS

Previously it was thought that the disease described herein could be due to an acute respiratory infection aggravated by the altitude. Later it was evident that disease of the lungs probably was an aggravating or a precipitating cause in some cases, but there were many instances in which an infection was not present. An acute infection can hardly be responsible for a disease that appears shortly after arrival to a high altitude and disappears as the patient descends to sea level.

In 1903 Mosso[5] observed mild pulmonary edema in dogs exposed to low barometric pressures. In 1907 Spehl and Desguin[6] found in acute experiments that the amount of blood in the lungs of rabbits increased when the animal was transported from the low levels to an altitude of 3,000 meters (9,900 feet). In 1913 Heger[7] observed pulmonary congestion and dilatation of the right ventricles in rabbits and guinea pigs when the barometric pressure went down rapidly to 500 mm. or less. Von Euler and Liljestrand[8,9] produced pulmonary hypertension in animals by short periods of hypoxia. Similar findings have been reported in man by Motley et al.,[10] Doyle et al.[11] and others.[12] The cardiac output in the normal subjects as well as in animals can increase with hypoxia.[13–15] Lewis and Gorlin,[16,17] in experiments performed on anesthetized dogs breathing a mixture of 10 per cent oxygen which is equivalent to an altitude of approximately 5,400 meters (18,000 feet), observed that both cardiac output and work of the left ventricle increased but mean left atrial pressure remained normal even in experiments that lasted eight hours. The important observations of Theilen, Gregg and Rotta[18] suggest that for comparable amounts of external work at sea level the heart of the native at high altitude responds with greater effort than the heart of the native sea level dweller. These authors believed that some of their figures approximated the maximum effort of the normal left ventricle. Besides these observations in relation to general circulation, there is experimental evidence that when the oxygen tension decreases the pulmonary lymph flow increases.[19,20]

The foregoing observations clearly indicate the importance of altitude in relation to the circulatory system. Nevertheless, the mechanism responsible for the pulmonary edema described here is not clear. It is difficult to understand why the same subject at the same altitude may one time have pulmonary edema and in other circumstances may feel well and remain asymptomatic. It is also difficult to interpret why pulmonary edema frequently occurred not only in normal and young people but also in those who, until a few days previously, had been living in and adapted to high altitude. These observations suggest that besides the circulatory changes that may be present there must be a variable factor or factors participating in the adaptation to high altitude. Some of the cases studied here indicate that after ten to fifteen days at sea level the mechanism by which human subjects are adapted to high altitude may be lost.

It is rather surprising that in our series of twenty-seven cases most subjects were young. The average age was twenty-five years and the oldest were forty-six and fifty-three years old. In Bardales'[4] twelve cases the oldest was

forty-four years and in Lizarraga's[3] seven cases the oldest was thirty-three. Considering the large number of people of different ages going to the highlands, this is not merely coincidental and a factor in relation to age seems to be important.

As emphasized, respiratory infections seem to be an aggravating or predisposing factor. In four cases the x-ray abnormalities were observed mainly in one lung. These observations suggest that the condition of the lungs may well play an important role.

## Summary

Twenty-seven cases of pulmonary edema of high altitude are reported. The disease occurred at an altitude of 3,000 meters (9,900 feet) or higher. Pulmonary edema of high altitude was observed in persons with normal hearts and often in young subjects. It occurred during the first trip, or in one or more of the several trips, made to the higher altitude. Several patients were symptom free in previous and subsequent trips to the same altitude. The disease was often observed in normal subjects adapted to the altitude going back to the highlands after spending a variable length of time at sea level. Respiratory infections were an aggravating or precipitating factor.

Pulmonary edema of high altitude was usually preceded by symptoms which, as a rule, appeared shortly after arrival at the high elevation. The knowledge of the premonitory symptoms is important to prevent death. The treatment of choice is oxygen or, when possible, descent to lower altitudes or sea level.

The cause of pulmonary edema of high altitude is obscure. The various possible mechanisms are briefly discussed.

## Acknowledgment

We express our thanks to Dr. Simon Dack for his valuable help in reviewing the manuscript and to Prof. P. Rijlant, Director of the Institute Solvay, for the early references listed. We also express our thanks to Dr. Jorge Rodríguez-Larrían for permission to publish Case 23.

## References

1. Hurtado, A. Aspectos Fisiopatólogicos y Patológicos de la Vida en la Altura, p. 30. Lima, 1937. Rímac S.A.
2. Lundberg, E. A. Conferencia en la Asociación Médica de Yauli. 1952.
3. Lizarraga, L. Soroche agudo: edema agudo del pulmón. *An. Fac. med. Lima*, 38: 244, 1955.
4. Bardales, A. Algunos casos de edema pulmonar agudo por soroche grave. *An. Fac. med. Lima*, 38: 232, 1955.
5. Mosso, A. L'Uomo sulle Alpi. Milano, 1909. Fratelli Treves.
6. Spehl, P. and Desguin, E. Influence de la depression barometrique sur la quantite de sang contenu dans les poumons. *Arch. ital. de Biol.*, 51: 1, 1907.
7. Heger, P. Altitude et coeur droit. *Travaux du Laboratoire de Physiol. Inst. Solvay*, 20: 1, 1913.
8. Von Euler, U. S. and Liljestrand, G. Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol. Scandinav.*, 12: 301, 1946.
9. Liljestrand, G. Regulation of pulmonary arterial blood pressure. *Arch. Int. Med.*, 81: 162, 1948.
10. Motley, H. L., Cournand, A., Himmelstein, A. and Dresdale, D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am. J. Physiol.*, 150: 315, 1947.
11. Doyle, J. T., Wilson, J. S. and Warren, J. V. The pulmonary vascular responses to short-term hypoxia in human subjects. *Circulation*, 5: 263, 1952.
12. Dexter, L. Cor pulmonale cronico con hypoxia o sin ella. *Arch. Inst. cardiol., Mexico*, 22: 655, 1952.
13. Harrison, T. R. and Blalock, A. The regulation of circulation. VI. The effects of severe anoxemia of short duration on the cardiac output of morphinized dogs and trained unnarcotized dogs. *Am. J. Physiol.*, 80: 168, 1927.
14. Keys, A., Stapp, J. P. and Violante, A Responses in size and efficiency of the human heart to acute alteration in the composition of the inspired air. *Am. J. Physiol.*, 138: 763 1943.
15. Starr, I. and McMichael, M. Oxygen transport, circulation and respiration in healthy subjects at simulated altitudes of 16,000 to 18,000 feet. *J. Appl. Physiol.*, 1: 430 1948.
16. Lewis, B. and Gorlin, R. Effects of hypoxia on pulmonary circulation of the dog. *Am. J. Physiol.*, 170: 574, 1952.
17. Gorlin, R. and Lewis, B. Circulatory adjustments to hypoxia in dogs. *J. Appl. Physiol.*, 7: 180, 1954.
18. Theilen, E. O., Gregg, D. E. and Rotta, A. Exercise and cardiac work response at high altitude. *Circulation*, 12: 383, 1955.
19. Warren, M. F., Peterson, D. K. and Drinker, C. K. The effects of heightened negative pressure in the chest, together with further experiments upon anoxia in increasing the flow of lung lymph. *Am. J. Physiol*, 137: 641, 1942.
20. Beznack, A. B. and Liljestrand, G. The effect of variation in oxygen tension on the lymph flow. *Acta Physiol. Scandinav.*, 17: 170, 1949.

# Cardiac Index in Ambulatory Patients Estimated by Precordial Dilution Curves*

KENNETH M. CAMPIONE, M.D., IRENE J. ANDAY, M.D., MARIA SERRATTO, M.D. *and* DAVID P. EARLE, M.D., WITH THE TECHNICAL ASSISTANCE OF JOLANTA MUNCH, M.S.

Chicago, Illinois

MUCH VALUABLE INFORMATION has been obtained from the measurement of cardiac output in disease. The method based on the Fick principle has been standard for some years but unfortunately it requires cardiac catheterization. The dye dilution technic of Hamilton[1,2] also has been established as an accurate method but requires arterial cannulation and analysis of many samples. Recently, several investigators,[3–6] extending the preliminary observations of Prinzmetal et al.,[7] have developed a method for estimating cardiac output by external counting of radioactivity over the precordium following an intravenous injection of $I^{131}$ labeled human serum albumin. This technic is simple and causes little or no discomfort to the patient. It is ideally suited for serial observations in a cardiovascular outpatient population.

The present paper is an analysis of 429 observations of cardiac index measured by the external counting technic in 240 ambulatory patients with and without evidence of heart disease. Some consideration also is given to the shape of time-concentration curve of radioactivity or "radiocardiogram." Cardiac indices and radiocardiograms in ambulatory patients with hypertension, coronary artery disease or valvular heart disease, with and without congestive heart failure, are considered briefly.

## METHODS

The ambulatory patient comes to the laboratory without any special preparation. The patient lies down for five to ten minutes prior to the test but no effort is made to achieve basal conditions. With the patient supine, a scintillation probe† containing a 1 by 1 inch sodium iodide detector crystal and a nose piece with a $1^5/_{16}$ inch aperature mounted on an adjustable stand‡ is positioned over the midsternum opposite the third interspace. The scintillation probe is connected through a rate meter§ (time constant = 0.5 second, operating voltage = 1,150, and counting range = 100 K) to a rectilinear galvanometric recorder‖ (graph speed = 15.2 cm. per minute). Twenty to fifty (usually 30) microcuries of $I^{131}$ labeled human serum albumin in 1 ml. saline in a tuberculin syringe (delivery error of less than 1 per cent in thirty measurements) are injected as rapidly as possible into an antecubital vein.

Precise positioning of the probe apparently is not important.[5,8] In our own laboratory variations in position of the scintillation probe appeared to have little effect on the cardiac index despite moderate variations in the shape of the radiocardiogram. Right vs. left parasternal line, midsternal vs. right or left parasternal line, second vs. third or fourth rib interspace and anterior vs. posterior positions were compared in twenty-one patients. The mean cardiac index in the first positions was 3.28 and in the second positions was 3.30 ($p > 0.5$).

Venous blood is obtained at ten and twenty minutes after the injection of radioactive iodinated human serum albumin for determination of blood volume. Radioactivity of the venous blood is measured in a well counter for calculation of blood volume. Cardiac output is calculated from the radiocardiogram and the blood volume as described by Zipf.[6]

All cardiac output values in this paper are presented as the cardiac index (L. per minute per square meter of body surface area).

As compared to 429 cardiograms from which cardiac indices could be calculated, only thirty-one

† Versatile Scintillation Counter Model DS5, Nuclear Instrument and Chemical Corp., Chicago, Illinois.

‡ Stand and holder, Nuclear Instrument and Chemical Corp., Chicago, Illinois.

§ Analytical Count Rate Meter Model 1620, Nuclear Instrument and Chemical Corp., Chicago, Illinois.

‖ Rectilinear Galvanometric Recorder, Houston Technical Laboratories, Houston, Texas.

* From the Departments of Medicine, Northwestern University Medical School and the Passavant Memorial Hospital, Chicago, Illinois. Supported in part by grants from the Chicago Heart Association, the Otho S.A. Sprague Foundation and the U. S. Public Health Service (H-1890).

TABLE I
Types of Valvular Lesions

| Valvular Lesion | Patients Studied (no.) |
|---|---|
| Mitral stenosis | 15 |
| Mitral insufficiency | 11 |
| Mitral stenosis and insufficiency | 3 |
| Aortic stenosis | 5 |
| Aortic insufficiency | 3 |
| Aortic stenosis and insufficiency | 1 |
| Combined mitral and aortic lesions | 8 |
| Total | 46 |

instances were encountered in which the curves were of such poor amplitude that reasonable extrapolation was impossible. In all but seven of these instances earlier or later attempts were successful. In four of the seven patients a second attempt was not made. Except in the few instances mentioned previously, the first tracings obtained were successful. When more than one radiocardiogram was obtained in a patient, only the cardiac index calculated from the first successful tracing was used in computing the group averages (vide infra).

## Clinical Material

Our group of 240 cases was composed of forty-eight normal subjects, seven "nearly normal" subjects, seventy-one patients with hypertensive disease, forty-eight patients with coronary artery disease, forty-six patients with valvular heart disease, seven emphysematous patients and thirteen patients with miscellaneous diseases. The "nearly normal" group included one patient under investigation for possible mild rheumatic fever, two patients with first degree heart block of unknown etiology, two patients with bundle branch block of unknown etiology, one psychiatric patient digitalized for reasons unknown and one patient with a transverse diameter of the heart on roentgenogram 15 per cent above the mean estimated normal but no other evidence of heart disease. Fifteen of the forty-eight patients in the coronary artery disease group also had arterial hypertension. Of the seven patients with emphysema, three also had some evidence of myocardial involvement (due to presumed coronary artery disease in one patient and to probable cor pulmonale in the other two). Two of these also manifested congestive heart failure. The miscellaneous group included three patients with probable right-sided aorta (diagnosed on routine chest roentgenogram), three patients with interatrial septal defects (two confirmed at surgery and the other diagnosed on the basis of catheterization data), two patients with clinically presumed interventricular septal defects, one patient with coronary artery disease and ascites attributed to cirrhosis, one patient with hypertensive disease and anasarca which was part of a nephrotic syndrome, one patient with coronary artery disease and Paget's disease, one patient with hypothyroidism and one patient with moderate hyperthyroidism. The specific valve lesions in the forty-six patients with valvular heart disease are listed in Table I.

## Results

### NORMAL SUBJECTS

The mean cardiac index in forty-eight subjects without evidence of hypertension, cardiovascular, renal or pulmonary disease was 3.51 L. per minute per square meter of surface area, with a standard deviation of 0.97 and a range

TABLE II
Cardiac Index in Normal Subjects

| Group | No. of Patients | Cardiac Index (L./min./M²) | | | No. with Cardiac Index Less than Mean | |
|---|---|---|---|---|---|---|
| | | Mean | S.D.* | p | Normal Minus 1 S.D. | Normal Minus 2 S.D. |
| Normal | 48 | 3.51 | 0.97 | ... | 6 | 0 |
| "Near" normal | 7 | 4.32 | ... | ... | 0 | 0 |
| Normal, under 40 years | 25 | 3.67 | 1.02 | ... | 3 | 0 |
| Normal, 40 and over | 23 | 3.33 | 0.92 | >0.2 | 3 | 0 |
| Normal, men | 32 | 3.48 | 1.00 | ... | 5 | 0 |
| Normal, women | 16 | 3.56 | 0.99 | >0.5 | 1 | 0 |

* In this and the following tables S.D. = standard deviation.

of 1.92 to 5.64 (Table II). Thirty-one of the values fell between 2.54 and 4.48. The mean cardiac index in the twenty-five subjects ranging in age between twelve and thirty-nine years was 3.67 as compared to 3.33 in twenty-three subjects forty to eighty-three years old ($p > 0.2$). The mean value in thirty-two men was 3.48 and in sixteen women was 3.56. ($p > 0.5$). None of these differences are statistically significant. In the "nearly normal" group of seven patients, the mean cardiac index was 4.32 L. per minute.

The mean normal cardiac index observed in this study is in good agreement with values recorded in the literature (Table III).

### COMPARISON WITH OTHER METHODS

Unfortunately, our local circumstances have precluded an extensive comparison of the external counting technic with the Fick or direct arterial sampling methods. In the nine simultaneous comparisons with the Fick method that we have been able to make, five were in patients with some degree of valvular insufficiency, one in a patient with pure mitral stenosis, two in patients with atrial septal defects and one in a patient with a right-sided aorta. The smallest difference was 1 per cent in a patient with a moderate aortic stenosis and insufficiency and the largest was 64 per cent in a patient with an atrial septal defect. The average individual difference between the two methods was 29 per cent. In all but one instance the cardiac index based on external counting was lower than the cardiac index computed on the Fick principle. Lesions such as valvular insufficiency or septal defects produce distorted radiocardiograms which Huff[8] states may result in erroneous cardiac indices due to "repetitive recording of isotope in the same channel or chamber." Certainly our observations bear this out. Hence, in the presence of valvular insufficiency or a shunt the "cardiac index" calculated from the radiocardiogram may be inaccurate and falsely low.

Huff et al.[5] reported good correlation between simultaneously determined Fick and external isotope detection cardiac indices in seven determinations in five presumably normal subjects. Scheimer, Lovejoy and Yu[15] more recently reported twenty-six simultaneous comparisons between the Fick and external detection method in which the per cent difference between the methods ranged from 0.2 to 41.7. In addition, they reported a difference of 0 to 28 per cent when external detection was compared to direct arterial sampling in forty-four instances. Most of their patients had some form of valvular disease.

### DUPLICATE MEASUREMENTS

In seventy-nine subjects, some of whom had heart disease, duplicate measurements of cardiac index were made twenty minutes apart. The mean value for the initial measurements was 3.32 L. per minute as compared to 3.06 for the second measurements, a small but highly significant statistical difference ($p < 0.001$ by the individual paired comparison method[16]). In fifty-two of the seventy-nine comparisons

TABLE III
Normal Cardiac Index Reported in the Literature

| Authors | Method | No. of Patients | | Cardiac Index (L./min./M²) Mean | S.D. |
|---|---|---|---|---|---|
| Cournand et al.[9] | Fick | Normal men | 13 | 3.12 | 0.40 |
| | | "Hospital normals" | 34 | 3.32 | 0.59 |
| Chapman et al.[10] | Fick | | 7 | 3.27 | 0.78 |
| Dexter et al.[11] | Fick | | 7 | 3.79 | 0.79 |
| Doyle et al.[12] | Fick | | 34 | 3.80 | 1.03 |
| | Dye | | 10 | 2.85 | 0.56 |
| Freis et al.[13] | Dye | | 7 | 4.20 | 0.76 |
| Kowalski et al.[14] | Dye | | 12 | 3.76 | 0.65 |
| Huff[8] | External counting | Women | 28 | 3.30 | 0.8 |
| | | Men | 36 | 3.60 | 0.8 |
| | | Total | 64 | 3.47 | ... |
| Zipf et al.[6] | External counting | | 98 | 3.64 | 0.9 |
| Present series | External counting | | 48 | 3.51 | 0.97 |

TABLE IV
Cardiac Index in Congestive Heart Failure

| Group | No. of Patients | Cardiac Index (L./min./M²) | | | No. with Cardiac Index Less than Mean | |
|---|---|---|---|---|---|---|
| | | Mean | S.D. | p | Normal Minus 1 S.D. | Normal Minus 2 S.D. |
| Normal | 48 | 3.51 | 0.97 | ... | 6 | 0 |
| CHF* | | | | | | |
| All | 64 | 2.45 | 1.24 | <0.001 | 36 | 13 |
| Hypertension | 14 | 2.71 | 0.94 | <0.01 | 6 | 2 |
| Coronary heart disease | 23 | 2.62 | 0.93 | <0.001 | 11 | 4 |
| Valvular heart disease | 27 | 2.16 | 0.82 | <0.001 | 19 | 7 |
| CHF | | | | | | |
| Hyp. + Cor. | 37 | 2.63 | 0.93 | ... | 17 | 6 |
| Valvular | 27 | 2.16 | 0.82 | <0.05 | 19 | 7 |
| CHF | | | | | | |
| Controlled | 37 | 2.68 | 0.98 | ... | 18 | 5 |
| Overt | 27 | 2.13 | 0.73 | <0.025 | 18 | 8 |
| CHF | | | | | | |
| Overt | 10 | 2.07 | ... | ... | 6 | 4 |
| Controlled (Same patients) | 10 | 2.87 | ... | <0.025† | 5 | 0 |
| CHF | | | | | | |
| First measurement | 13 | 2.19 | ... | ... | 8 | 2 |
| Later measurement (No change in clinical status) | 13 | 2.87 | ... | >0.4† | 6 | 0 |

* CHF = Congestive heart failure.
† By paired comparison.

the second value was less than the first. In contrast, cardiac indices measured weeks to months apart in twenty-three subjects whose clinical status did not change in the interim did not differ significantly ($p > 0.2$).

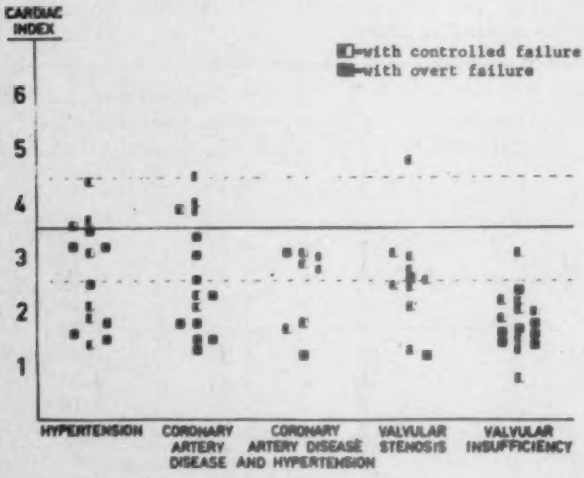



FIG. 1. Cardiac index in patients with congestive heart failure. (The normal mean cardiac index is indicated by a solid line with one standard deviation represented by interrupted lines.)

CONGESTIVE HEART FAILURE

The mean cardiac index in sixty-four ambulatory patients with heart disease and congestive heart failure either in the past or at time of study (Table IV, Fig. 1) was 2.45 L. per minute, a value significantly less than normal ($p < 0.001$). The cardiac index in patients with congestive heart failure (past or present) was significantly less than normal no matter what the etiology of the heart disease. Probably because valvular incompetence may distort the radiocardiogram and lead to an erroneously low value, the calculated cardiac index in the patients with valvular heart disease was less than in those with congestive heart failure due to hypertensive or coronary artery heart disease ($p < 0.05$). Emphysematous patients and those with miscellaneous conditions were not included in this evaluation.

*Overt vs. Controlled Congestive Failure:* The patients were divided into two groups according to whether the signs or symptoms of congestive failure were considered to be overt or controlled by therapy. Dyspnea on less than one flight of stairs, orthopnea, venous distension, hepato-

TABLE V
Cardiac Index in Hypertensive Vascular Disease

| Group | No. of Patients | Cardiac Index (L./min./M²) | | | No. with Cardiac Index Less Than Mean | |
|---|---|---|---|---|---|---|
| | | Mean | S.D. | p | Normal Minus 1 S.D. | Normal Minus 2 S.D. |
| Normal | 48 | 3.51 | 0.97 | ... | 6 | 0 |
| HVD* | | | | | | |
| All | 71 | 3.23 | 1.21 | >0.2 | 21 | - |
| No CHF† | | | | | | |
| All | 57 | 3.25 | 1.24 | >0.4 | 15 | 5 |
| Borderline | 11 | 4.25 | 1.56 | <0.05 | 2 | 1 |
| Systolic | 21 | 3.35 | 1.20 | >0.5 | 6 | 2 |
| Diastolic | 25 | 2.96 | 0.93 | <0.025 | 7 | 2 |
| No myocardial involvement | 30 | 3.65 | 1.27 | >0.5 | 6 | 2 |
| Myocardial involvement | 27 | 3.02 | 1.09 | >0.05 | 9 | 3 |
| HVD | | | | | | |
| No CHF | 57 | 3.35 | 1.24 | ... | 15 | 5 |
| CHF | 14 | 2.71 | 0.94 | <0.1 | 6 | 2 |
| HVD | | | | | | |
| No CHF | | | | | | |
| Systolic | 21 | 3.35 | 1.20 | ... | 6 | 2 |
| Diastolic | 25 | 2.71 | 0.93 | >0.2 | 7 | 2 |
| HVD | | | | | | |
| No CHF | | | | | | |
| No myocardial involvement | 30 | 3.65 | 1.30 | ... | 6 | 2 |
| Myocardial involvement | 27 | 3.02 | 1.09 | >0.05 | 9 | 3 |

* HVD = hypertensive vascular disease.
† CHF = Congestive heart failure, past or present.

megaly and edema of the ankles were taken as signs of overt congestive failure in patients with heart disease, whether or not they were under treatment at the time of study. If these symptoms or signs had once been present but were absent at the time of study, the heart failure was considered to be controlled. Dyspnea on two flights and minimal hepatomegaly or a trace of edema of the ankles were permitted in this category. The mean cardiac index was 2.13 in the twenty-seven patients with overt congestive heart failure as compared to 2.68 in thirty-seven patients with "controlled" failure, a probably significant difference ($p < 0.025$). Cardiac index was measured in ten patients during overt failure and again when control of the symptoms and signs of failure had been achieved by treatment with digitalis, mercurials or oral diuretics. A mean cardiac index of 2.07 during overt failure was probably significantly different than the value of 2.87 observed during controlled failure ($p < 0.025$). In contrast, cardiac index did not change in thirteen patients with failure in whom the degree of signs and symptoms of failure persisted unchanged (3.19 vs. 2.87, $p > 0.4$).

HYPERTENSION

The mean cardiac index in seventy-one patients with hypertension (Table v, Fig. 2),

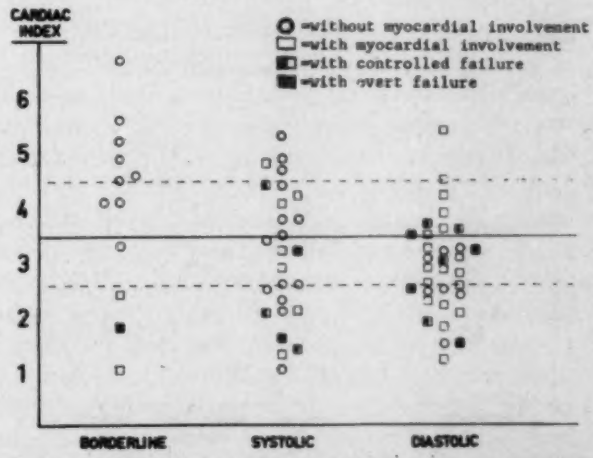



FIG. 2. Cardiac index in patients with hypertension. (Borderline hypertension = systolic pressure 140–160 mm. Hg, diastolic pressure 90–100. Systolic hypertension = systolic pressure >160; diastolic pressure <100. Diastolic hypertension = diastolic pressure >100.)

TABLE VI
Cardiac Index in Coronary Artery Disease

| Group | No. of Patients | Cardiac Index (L./min./M²) | | | No. with Cardiac Index Less Than Mean | |
|---|---|---|---|---|---|---|
| | | Mean | S.D. | p | Normal Minus 1. S.D. | Normal Minus 2 S.D. |
| Normal | 48 | 3.51 | 0.97 | ... | 6 | 0 |
| CAD* | | | | | | |
| All | 48 | 2.99 | 0.94 | <0.01 | 15 | 5 |
| No CHF† | | | | | | |
| All | 25 | 3.33 | 0.83 | >0.4 | 4 | 1 |
| Presumed | 4 | 2.86 | ... | ... | 1 | 0 |
| Angina | 10 | 3.55 | ... | ... | 0 | 0 |
| Infarct | 4 | 2.38 | ... | ... | 3 | 1 |
| Infarct and angina | 7 | 4.44 | ... | ... | 0 | 0 |
| CAD | | | | | | |
| No CHF | 25 | 3.33 | 0.83 | ... | 4 | 1 |
| CHF | 23 | 2.62 | 0.93 | <0.01 | 11 | 4 |

* CAD = coronary artery disease.
† CHF = congestive heart failure, past or present.

including fourteen who also had evidence of congestive heart failure, was 3.23, a value which was not significantly less than normal ($p < 0.2$). The mean cardiac index in the fifty-seven hypertensive patients who had never had symptoms or signs of congestive heart failure was 3.35, likewise a value not significantly less than normal ($p < 0.4$). Nevertheless, fifteen (twenty-six per cent) of these patients had cardiac indices that fell below the mean normal value minus one standard deviation, as compared to only 12 per cent of the normal subjects. Five of the hypertensive patients had values that fell below the mean normal minus two standard deviations.

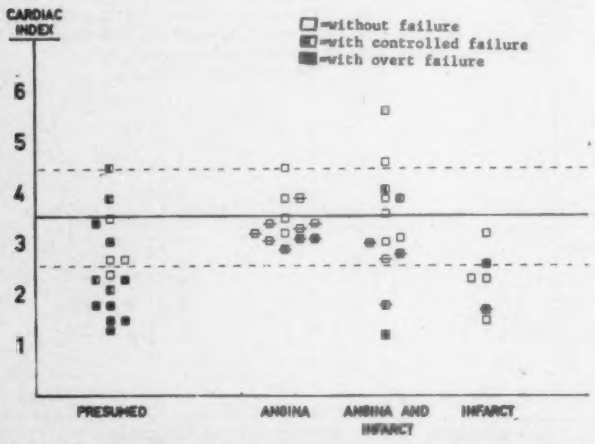



FIG. 3. Cardiac index in coronary artery disease. (Presumed = patients assumed to have coronary disease by exclusion of other etiologies. Coronary disease patients also having systolic or diastolic hypertension are indicated by a transverse line.)

*Types of Hypertension:* Blood pressure readings measured once or twice a month during the year preceding cardiac index determination were averaged. The patients were divided into three groups according to the degree of hypertension. Borderline hypertension was defined as average systolic pressure between 140 and 160 mm. Hg and average diastolic pressure between 90 and 100 mm. Hg; systolic hypertension as average systolic pressure greater than 160 mm. Hg and diastolic pressure less than 100; and diastolic hypertension as average diastolic pressure greater than 100 mm. Hg.

The mean cardiac index in eleven patients with borderline hypertension without heart failure was 4.25, a value greater than normal ($p < 0.05$). The mean cardiac index in twenty-one patients with systolic hypertension without heart failure was 3.35, not significantly different than normal ($p > 0.5$). However, the mean cardiac index in twenty-five patients with diastolic hypertension but without heart failure was 2.96, a value probably significantly below normal ($p < 0.025$). The cardiac index in nineteen of the twenty-five patients with diastolic hypertension was less than the mean normal value; however, it fell below the mean normal minus one standard deviation in seven, or 28 per cent.

TABLE VII
Cardiac Index in Valvular Heart Disease

| Group | No. of Patients | Cardiac Index (L./min./M²) | | | No. with Cardiac Index Less Than Mean | |
|---|---|---|---|---|---|---|
| | | Mean | S.D. | p | Normal Minus 1 S.D. | Normal Minus 2 S.D. |
| Normal | 48 | 3.51 | 0.97 | ... | 6 | 0 |
| VHD* | | | | | | |
| All | 46 | 2.55 | 1.24 | <0.001 | 27 | 8 |
| No CHF† | | | | | 8 | 1 |
| All | 19 | 3.10 | 1.54 | >0.1 | 8 | 1 |
| No myocardial involvement | 7 | 2.82 | 1.38 | >0.1 | 4 | 0 |
| Myocardial involvement | 12 | 3.26 | 1.65 | >0.4 | 4 | 1 |
| VHD | | | | | | |
| No CHF | 19 | 3.10 | 1.54 | ... | 8 | 1 |
| CHF | 27 | 2.16 | 0.82 | <0.025 | 19 | 7 |
| VHD | | | | | | |
| No CHF | | | | | | |
| No myocardial involvement | 7 | 2.82 | 1.38 | ... | 4 | 0 |
| Myocardial involvement | 12 | 3.26 | 1.65 | >0.5 | 4 | 1 |
| VHD | | | | | | |
| No CHF | | | | | | |
| Stenosis | 9 | 3.91 | 1.80 | ... | 2 | 0 |
| Insufficiency | 10 | 2.36 | 0.81 | <0.025 | 6 | 1 |
| VHD | | | | | | |
| CHF (controlled) | | | | | | |
| Stenosis | 9 | 2.77 | 0.94 | ... | 3 | 1 |
| Insufficiency | 9 | 1.94 | 0.65 | <0.05 | 8 | 3 |

* VHD = valvular heart disease.
† CHF = congestive heart failure, past or present.

*Associated Myocardial Involvement:* The patients with hypertension were further classified on the basis of the presence or absence of "myocardial involvement." Myocardial involvement was considered to be present when the transverse diameter of the heart on the roentgenogram exceeded the mean normal value by more than 15 per cent, when significant abnormalities were noted on the electrocardiogram or when evidence of myocardial infarction, angina pectoris or congestive heart failure was obtained. The mean cardiac index in thirty patients with hypertension (nine borderline, fourteen systolic and seven diastolic) but without myocardial involvement was 3.65 L. per minute, a value not significantly different from normal ($p > 0.5$). The mean cardiac index of 3.02 observed in twenty-seven hypertensive patients (two borderline, seven systolic, eighteen diastolic) with myocardial involvement but without evidence of heart failure did not quite differ significantly from normal ($p > 0.05 < 0.1$). Nine (33 per cent) of this group had values less than the mean normal minus one standard deviation; three fell below the normal minus two standard deviations, despite the absence of heart failure.

### CORONARY ARTERY DISEASE

Definite evidence of myocardial infarction in the past, typical angina pectoris, or both, were considered to be unequivocal evidence of coronary artery disease in thirty-two patients (Table VI, Fig. 3). Fifteen of these patients also had systolic or diastolic hypertension. Coronary artery disease was presumed (possibly erroneously in some instances) to be present in another sixteen patients who had heart failure, significant cardiac enlargement or electrocardiographic abnormalities (alone or in combination) in the absence of hypertension or other known etiology of heart disease. The mean cardiac index for the entire group of forty-eight patients was 2.99 L. per minute, a value significantly less than normal ($p < 0.01$). In contrast, the mean cardiac index in twenty-

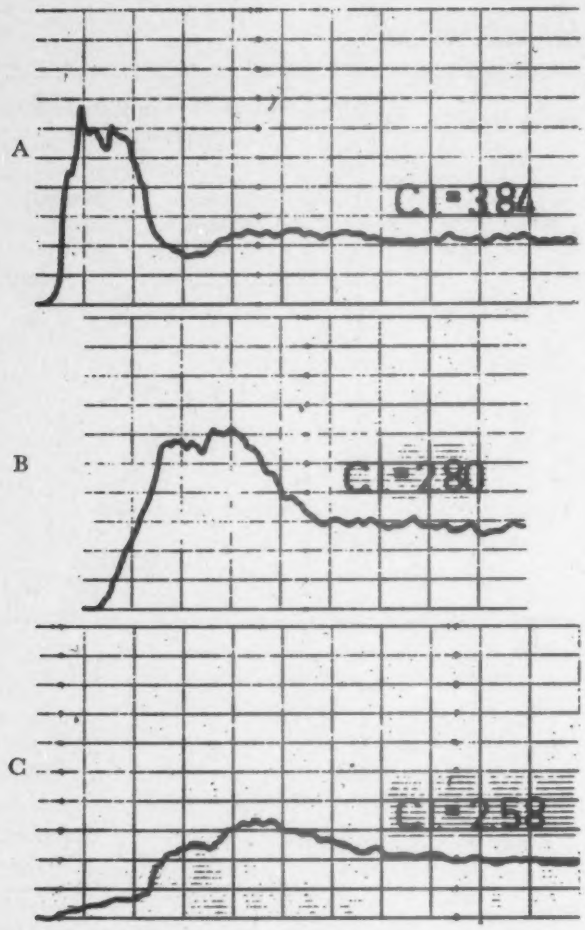



FIG. 4. Typical radiocardiograms. A, normal slim appearance with steep up- and downslopes. B, questionable tracing with blunting of the peaks and wider general appearance due to more gentle downslope. C, abnormal curve with widened peaks of poor amplitude and marked prolongation of downslope.

five patients with definite or presumed coronary artery disease who never had evidence of heart failure was 3.33, which was not significantly below normal ($p > 0.4$).

The mean cardiac index in seven patients with coronary artery disease without congestive heart failure but with hypertension (three systolic, four diastolic) did not differ significantly from the cardiac index in fourteen patients with definite coronary artery disease who were not hypertensive. The number of patients among the subgroups of coronary artery disease without congestive heart failure are too small to provide meaningful information.

### VALVULAR HEART DISEASE

As previously mentioned, cardiac index estimated by the external counting technic in patients with valvular insufficiency is subject to error due to distortion of the radiocardiogram. Nevertheless, mean cardiac index calculated in twenty-seven patients with valvular heart disease who in the past or at the time of study had congestive heart failure was 2.16 L. per minute (Table VII). This value was significantly less than that observed in nineteen patients with valvular heart disease who never had had congestive heart failure ($p < 0.025$). Among the various etiologies of congestive heart failure, that due to valvular disease was associated with the lowest cardiac index (Table IV, Fig. 1). Although the mean cardiac index of 3.1 L. per minute in nineteen patients with valvular heart disease but without congestive heart failure did not differ significantly from normal ($p > 0.1$), eight patients had values below the mean normal minus one standard deviation. Among these patients without congestive heart failure, nine with pure valvular stenosis had a mean cardiac index of 3.91 L. per minute, a value probably significantly greater than the mean cardiac index of 2.36 in the ten patients with valvular insufficiency ($p < 0.025$). Six of the latter had values less than the mean normal minus one standard deviation.

At the time of study, signs and symptoms of prior congestive failure were "controlled" in eighteen patients with valvular heart disease. Again, the mean cardiac index in the nine patients with pure stenosis probably significantly exceeded that in the nine patients who had valvular insufficiency ($p < 0.05$). Eight of the latter had indices that fell below the mean normal minus one standard deviation.

### FORM OF RADIOCARDIOGRAM

The normal radiocardiogram (Fig. 4, top) exhibited rather steep up- and downstrokes and a generally slim appearance Often two distinct spikes were present, presumably representing passage of the radioactive bolus through the right and left sides of the heart, respectively. The double spike was not always present in normal tracings. This feature probably was influenced by the relative positions of the scintillation probe and the heart. Radiocardiograms obtained in overt congestive heart failure (Fig. 4, bottom) and in certain valvular diseases of the heart exhibited decreased amplitude, slow up- and downstrokes and a blunting of the demarcation between the right and left spikes when present. The present evaluation of the form of radiocardiogram was subjective. Be-

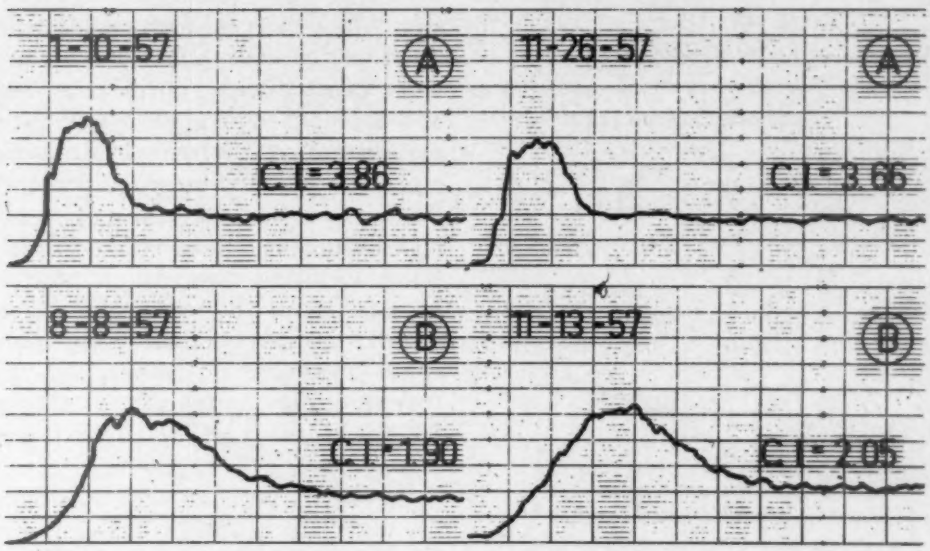



FIG. 5. Successive radiocardiograms in same patient. *Successive tracings* showing constancy of pattern without change in clinical condition. *Upper tracings* (A) were obtained on the same patient with an interval of ten and one-half months. *Lower tracings* (B) obtained on another patient are separated by a three month interval.

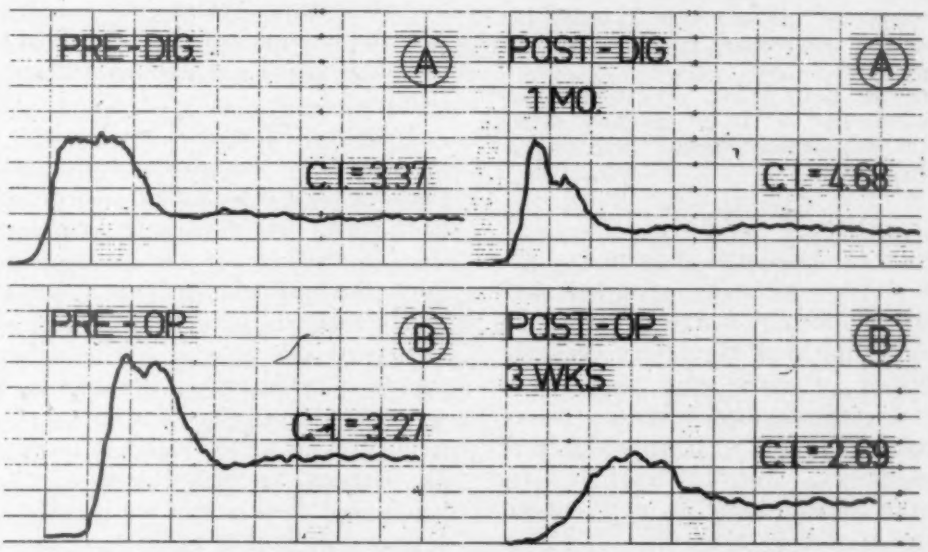



FIG. 6. Effect of therapy on radiocardiograms. A, *upper tracings* taken before and after digitalization illustrating change in curve contour as well as increase in cardiac index. B, *lower tracings* taken before and three weeks after mitral valvotomy, showing definite alteration in appearance.

cause of this an unfortunately large number of tracings were classified as "borderline" (Fig. 4, middle). Nevertheless, the form of the radiocardiogram remained constant in a given patient over considerable periods of time (Fig. 5). Infrequently (two of ten patients), a change from overt to controlled congestive heart failure was associated with an improvement in radiocardiogram appearance (Fig. 6A). Postvalvular commissurotomy tracings revealed a definite alteration in appearance when compared to preoperative tracings in two of eight patients (Figure 6B). Seven of these patients had mitral stenosis, one had aortic stenosis.

*Analysis of Tracings:* A qualitative analysis of the first radiocardiograms in our 240 patients is presented in summary form in Table VIII. This analysis was made without knowledge of the clinical data. One hundred tracings were classified as normal, fifty-six as borderline

TABLE VIII
Qualitative Analysis of Form of Radiocardiogram

| Group of Patients | Radiocardiogram Form | | | |
|---|---|---|---|---|
| | Normal | Borderline | Abnormal | Total |
| Normal | 33 | 8 | 7 | 48 |
| "Near" normal | 5 | 1 | 1 | 7 |
| Emphysema | 1 | 1 | 0 | 2 |
| Miscellaneous | 2 | 0 | 4 | 6 |
| HVD, no Myo, no CHF | 17 | 7 | 6 | 30 |
| VHD, no Myo, no CHF | 3 | 2 | 2 | 7 |
| Myo, No CHF | 28 | 22 | 23 | 73 |
| CHF | 11 | 15 | 41 | 67 |
| Totals | 100 | 56 | 84 | 240 |

NOTE: Patients in the emphysema, miscellaneous, hypertensive or valvular heart disease group are included under "myocardial involvement" or "congestive heart failure," if any of these conditions were present. "Coronary artery disease" patients were all considered to have "myocardial involvement," with or without "congestive heart failure."

CHF = congestive heart failure. HVD = hypertensive vascular disease. CAD = coronary artery disease. VHD = valvular heart disease. Myo = myocardial involvement.

and eighty-four as definitely abnormal. Review of the clinical protocols revealed that thirty-three of the normal tracings were from patients without clinical or laboratory evidence of cardiovascular disease, five were from "near" normal subjects and seventeen were from hypertensive patients without evidence of cardiac involvement. Normal tracings also were obtained in six additional patients without evidence of myocardial involvement. Twenty-eight of the normal tracings occurred in patients with some evidence of myocardial disease but without congestive heart failure, while only eleven of the normal tracings occurred in patients who had had congestive heart failure either in the past or present. Among the fifty-six patients with borderline radiocardiograms, eight were normal and one was a "near" normal, while twenty-two had evidence of myocardial disease and fifteen had clinical congestive heart failure. Seven had hypertensive disease without evidence of myocardial involvement, two had valvular insufficiency and one was an emphysematous patient without detectable myocardial disease. Of the eighty-four patients with radiocardiograms classified as definitely abnormal, seven had no obvious heart disease, one was a "near" normal and six had hypertension without evidence of myocardial involvement. Abnormal tracings also were obtained in two patients with valvular disease (one had valvular stenosis alone and one had insufficiency), in two patients with right-sided aorta, in one with hypothyroidism and in one with hyperthyroidism, all without myocardial involvement. The remainder had either evidence of myocardial disease alone (twenty-three patients) or congestive heart failure in the past or present (forty-one patients).

Of twenty patients with pure valvular stenosis, nine had normal tracings (four with heart failure), five had abnormal tracings (four with congestive heart failure) and six had borderline tracings (three with heart failure). Among twenty-six patients with valvular insufficiency (with or without associated stenosis) four had normal tracings, three had borderline tracings (one with congestive heart failure) and nineteen had abnormal tracings (fifteen with heart failure).

*Prominent Fluctuation in Tracings:* We were impressed by the presence of substantial fluctuations on the initial downslope of the radiocardiogram and during the secondary recirculation in tracings of certain patients (Fig. 7). Such fluctuations were noted most frequently and clearly in patients with mitral, aortic or combined mitral and aortic valvular insufficiency (Table IX). Prominent fluctuations were noted in sixteen of twenty-six patients with clinical evidence of valvular insufficiency with or without associated stenosis. In contrast, prominent fluctuations were noted in the tracings of only four of twenty patients with purely stenotic valvular lesions. However, sizable fluctuations were noted in the tracings of three of forty-eight normal subjects and in twenty-five of one hundred nineteen patients with hypertension or coronary artery disease. Among thirteen "miscellaneous" patients, two with right-sided aorta, two with atrial septal defects, one with hypothyroidism and one with Paget's disease had prominent fluctuations. Prominent fluctuations in one patient with atrial shunt decreased in amplitude after surgical closure of the defect.

Prominent fluctuations were noted in the tracings of twenty-four of sixty-six patients with congestive heart failure and in eleven of

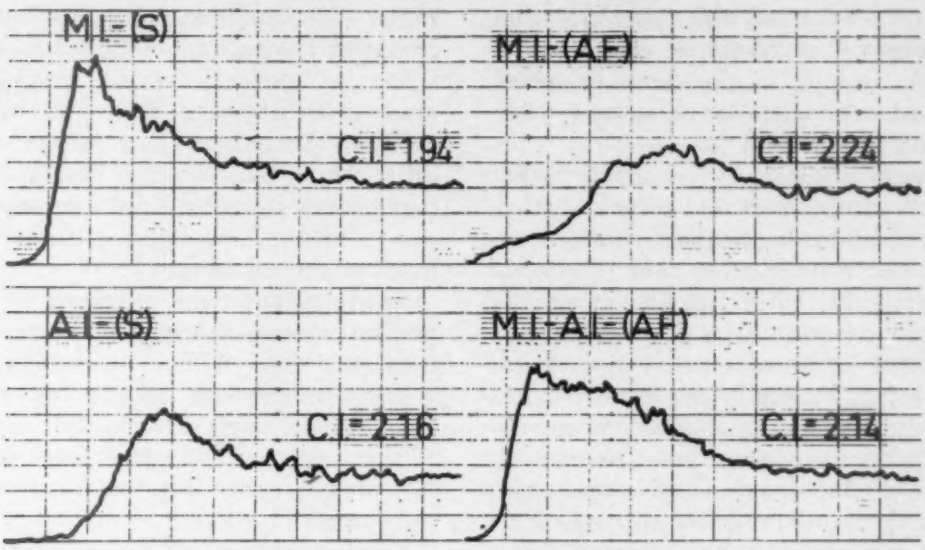



FIG. 7. Radiocardiograms in four cases of valvular insufficiency. Exaggerated fluctuations are seen on primary passage and secondary circulation curves. (MI = mitral insufficiency; AI = aortic insufficiency; S = sinus mechanism; AF = atrial fibrillation.)

eighteen with atrial fibrillation. All of the latter also had congestive heart failure.

The diagnosis of valvular disease and classification as to type was made clinically in twenty-four patients, after cardiac catheterization alone in nine patients and by cardiac catheterization and surgery in thirteen patients. Of the twenty-two patients with valvular disease confirmed by catheterization or catheterization and surgery, thirteen had pure stenosis (ten mitral and three aortic) and nine had some degree of valvular insufficiency (nine mitral, two aortic and two combined). Only two (one mitral and one aortic) of the thirteen patients with pure stenosis, as compared to seven (four mitral, one aortic and two combined) of the nine patients with valvular insufficiency had tracings with prominent fluctuations.

## COMMENTS

Simplicity and safety are two obvious advantages of the external counting technic for estimation of cardiac index. The method makes possible frequent serial observations in a large number of ambulatory patients, an approach to the study and definition of the natural history of cardiac disease not practical with other available technics. Likewise, the method should be applicable without hazard to critically ill hospitalized patients.

Our mean cardiac index in normal subjects is in agreement with reports of other investigators using a variety of technics. Results obtained with the external counting technic appear to be reasonably reproducible and internally consistent. Several investigators[5,15] have reported fairly good correlation in direct comparisons between cardiac indices estimated by the external counting technic and by the Fick or Hamilton methods. However, they all reported some rather marked individual discrepancies. In our own laboratory wide discrepancies were noted among nine simultaneous comparisons with the Fick method. Seven of these nine patients had cardiac lesions

TABLE IX

Correlation of Prominent Fluctuations in Radiocardiograms with Clinical Diagnosis

| Diagnosis | No. of Patients | | |
|---|---|---|---|
| | With Fluctuations | Without Fluctuations | Total |
| Normal | 3 | 45 | 48 |
| Near normal | 0 | 7 | 7 |
| Emphysema | 1 | 6 (2) | 7 (2) |
| Miscellaneous | 6* | 7† | 13 |
| Hypertensive vascular disease | 15 (5) [2] | 56 (9) [1] | 71 (14) [3] |
| Coronary artery disease | 10 (5) [1] | 38 (18) [3] | 48 (23) [4] |
| Valvular stenosis | 4 (2) [1] | 16 (9) [2] | 20 (11) [3] |
| Valvular insufficiency | 16 (12) [7] | 10 (4) [1] | 26 (16) [8] |
| Totals | 55 (24) [11] | 185 (42) [7] | 240 (66) [18] |

*Two patients with a right-sided aorta; two with atrial septal defect; one with hypothyroidism and one with Paget's disease.

† One patient with right-sided aorta; one with atrial septal defect; two with ventricular septal defects; one with cirrhosis; one with nephrotic syndrome; one with hypothyroidism.

Numerals in parentheses indicate number of cases with congestive heart failure.

Numerals in brackets are number of cases with atrial fibrillation.

(valvular insufficiency or septal defects) that might be expected to result in repetitive recording of the isotope in the same chamber, and hence, should lead to erroneously low calculated "cardiac indices."

Patients with evidence of congestive heart failure either in the past or present had a significant reduction in cardiac index, even though they were ambulatory and in general had less severe heart failure than those usually reported in the literature. In addition, cardiac index increased in association with clinical evidence of improvement in the cardiac status after treatment. The cardiac index in congestive heart failure was lower in patients with valvular heart disease than in those with hypertensive or coronary artery disease. Perhaps the presence of valvular insufficiency accounted in part for this observation. Perhaps, too, "functional" valvular insufficiency in patients with congestive heart failure due to other etiologies contributed in part to the observed reduction in cardiac index. The finding of an unusually low cardiac index in a patient with heart disease, with or without congestive heart failure, might lead one to suspect the presence of valvular insufficiency, organic or "functional."

Observation of cardiac index in patients with hypertension (without evidence of congestive failure in the past or present) revealed information not generally recognized. Most investigators have stated that the cardiac index is normal in hypertensive patients without congestive failure.[17–20] Often the type, severity and duration of the hypertension have not been specified. We have observed a significant increase in cardiac index in a group of eleven patients with "borderline" hypertension (systolic pressure 140 to 160, diastolic pressure 90 to 100 mm. Hg). Finally, mean cardiac index in patients with sustained diastolic hypertension (diastolic pressure greater than 100 mm. Hg) was significantly less than normal. The majority of these patients had some evidence of myocardial involvement (enlarged heart, electrocardiographic abnormalities, angina or past myocardial infarction). Varnauskas[21] reported normal cardiac indices in hypertensives "without pronounced left ventricular strain" and further stated that "cardiac index diminished fairly generally with increase of left ventricular strain." However, although his findings implied and perhaps forecast our results, his grouping was based on the criteria of the New York Heart Association with no clear-cut separation of patients with and without congestive heart failure. Our data reveal that hypertensive patients without heart failure and without myocardial involvement had normal cardiac indices while hypertensive patients with myocardial involvement, but without current or past evidence of congestive heart failure, had reduced cardiac indices.

Most patients with coronary artery disease and no evidence of congestive heart failure had cardiac indices within the normal range, especially those with angina. A few patients who had suffered myocardial infarction had rather marked reduction in cardiac index. No patients with recent myocardial infarcts were studied.

Patients with purely stenotic valvular lesions did not have reduced cardiac index values until congestive heart failure developed. However, as discussed previously, valvular insufficiency leads to erroneously low "cardiac indices" by the external counting technics, regardless of the presence or absence of congestive heart failure.

The form of the radiocardiogram was subjected to qualitative analysis. Radiocardiograms of abnormal hearts often appeared blunted and delayed. However, correlation of qualitative features with normal or abnormal cardiovascular states was by no means constant and was less reliable than the calculated cardiac index as an indicator of abnormal cardiac function.

Of special interest were prominent fluctuations on the descending limb of the radiocardiograms of patients with valvular insufficiency. We interpreted these "jiggles" as evidence of to and fro movement of blood through an incompetent valve. Such irregularities were uncommon in patients with purely stenotic valvular lesions. Possibly lesser degrees of valvular incompetence such as relative mitral insufficiency in hearts with left ventricular hypertrophy are at times of sufficient dynamic magnitude to account for the prominent fluctuations observed in the radiocardiograms of some of our patients with hypertensive or coronary heart disease. More data will be necessary to establish such findings as actual reflections of alterations in intracardiac dynamics and to establish their clinical usefulness.

The form of the primary passage curve was constant in serial radiocardiograms obtained from the same patient. However, the radiocardiogram appearance occasionally was al-

tered by medical or surgical events which might reasonably have been expected to influence cardiac dynamics.

Two lines of study in the use of radiocardiograms have developed. The first of these is exemplified by Huff et al.[8] who by means of greater collimation have obtained tracings from different parts of the chest wall. They have been able to relate differences in the appearance of simultaneous tracings from different areas of the chest to valvular or septal defects. Another group, exemplified by Shipley,[3] Zipf and coworkers[6] and ourselves, have used wide angle collimation. This approach is the simpler and allows use of a small dose of radioisotope. It is hoped that further study of the configuration of curves obtained from the general precordial area will allow detection of intracardiac defects.

## Summary

1. Four hundred and twenty-nine radiocardiograms were obtained in 240 ambulatory patients with and without heart disease by means of wide angle external counting over the precordium after the injection of radioactive iodinated human serum albumin into an antecubital vein. Cardiac index was calculated from the radiocardiogram and the blood volume. Only seven patients were encountered in whom a tracing adequate for calculation of cardiac index was not obtained.

2. A mean cardiac index of 3.51 L. per minute per square meter surface area with a standard deviation of 0.97 was derived from forty-eight persons without known cardiac or vascular disease. Cardiac indices were slightly but significantly lower when derived from radiocardiograms taken twenty minutes after the initial tests. By contrast, cardiac indices did not differ significantly when calculated from tracings made weeks to months apart in patients with stable cardiovascular systems.

3. A significant decrease in cardiac index was observed in patients with all types of heart disease who had congestive heart failure, whether overt or controlled.

4. In the absence of congestive heart failure, mean cardiac index was increased in patients with borderline hypertension, normal in those with systolic hypertension, and frequently reduced in those with sustained diastolic hypertension, especially when evidence of myocardial involvement also was present.

5. Cardiac index was usually normal in patients with coronary artery disease in the absence of congestive heart failure. Occasional reduction was seen in patients with old myocardial infarctions.

6. A probably significant decrease of cardiac index as measured by the external counting technic was observed in patients with valvular heart disease without congestive heart failure. Also, cardiac index in congestive heart failure due to valvular heart disease was lower than that due to other types of heart disease. Valvular insufficiency apparently leads to erroneously low values of cardiac index estimated by the external counting technic.

7. Classification of radiocardiograms according to qualitative features showed some correlation with cardiovascular status. Prominent fluctuations on the downslope were recognized most often in radiocardiograms of patients with valvular insufficiency. The appearance of the radiocardiogram maintained a constancy over considerable periods of time in the absence of marked change in cardiovascular status.

## References

1. Kinsman, J. M., Moore, J. W. and Hamilton, W. F. Studies on the circulation. I. Injection method: Physical and mathematical considerations. *Am. J. Physiol.*, 89: 322, 1929.
2. Moore, J. W., Kinsman, J. M., Hamilton, W. F. and Spurling, R. G. Studies on the circulation. II. Cardiac output determination. Comparison of the injection method with the direct Fick procedure. *Am. J. Physiol.*, 89: 331, 1929.
3. Shipley, R. A., Clark, R. E., Liebowitz, D. and Krohmer, J. S. Analysis of the radiocardiogram in heart failure. *Circulation Res.*, 1: 428, 1953.
4. Veall, N., Pearson, J. D., Hanley, T. and Lowe, A. E. A method for the determination of cardiac output (preliminary report). *Proc. Second Radioisotope Conference*, p. 183–192. Oxford, July 19–23, 1954. London, 1954. Butterworth's Scientific Publications.
5. Huff, R. L., Feller, D. D., Judd, O. J. and Bogardus, G. M. Cardiac output of men and dogs measured by in vivo analysis of iodinated (I-131) human serum albumin. *Circulation Res.*, 3: 564, 1955.
6. Zipf, R. E., McGuire, T. F., Webber, J. M. and Grove, G. R. Determination of cardiac output by means of external monitoring of radioisotope injected intravenously. *Am. J. Clin. Path.*, 28: 134, 1957.
7. Prinzmetal, M., Corday, E., Spritzler, R. J. and Fleig, W. Radiocardiography and its clinical application. *J.A.M.A.*, 189: 617, 1949.
8. Huff, R. L., Parrish, D. and Crockett, W. A study of circulatory dynamics by means of crystal radiation detectors on the anterior thoracic wall. *Circulation Res.*, 4: 395, 1957.
9. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF. and Richards, D. W., Jr. Measurement of cardiac output in man using the tech-

nique of catheterization of the right auricle or ventricle. *J. Clin. Invest.*, 24: 106, 1945.

10. Chapman, C. B., Taylor, H. L., Borden, C., Ebert, R. B. and Keyes, A. Simultaneous determination of the resting arteriovenous oxygen difference by the acetylene and direct Fick methods. *J. Clin. Invest.*, 29: 651, 1950.
11. Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R. and Sawyer, C. C. Effect of exercise on circulatory dynamics of normal individuals. *J. Appl. Physiol.*, 3: 439, 1951.
12. Doyle, J. T., Wilson, J. S., Estes, E. H. and Warren, J. V. The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. *J. Clin. Invest.*, 30: 345, 1951.
13. Freis, E. D., Schnaper, H. W., Johnson, R. L. and Schreiner, G. E. Hemodynamic alterations in acute myocardial infarction. I. Cardiac output, mean arterial pressure, total peripheral resistance, "central" and total blood volumes, venous pressure and average circulation time. *J. Clin. Invest.*, 31: 131, 1952.
14. Kowalski, H. J. and Abelmann, W. H. The cardiac output at rest in Laennec's cirrhosis. *J. Clin. Invest.*, 32: 1025, 1953.
15. Scheimer, B. F., Lovejoy, F. W. and Yu, P. N. Estimation of cardiac output from precordial dilution curves in patients with cardiopulmonary disease. *Circulation Res.*, 7: 595, 1959.
16. Snedecor, G. F. Statistical Methods. Ames, Iowa, 1956. The Iowa State College Press.
17. Bolomey, A. A., Michie, A. J., Michie, C., Breed, E. S., Schreiner, G. E. and Lauson, H. D. Simultaneous measurements of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension. *J. Clin. Invest.*, 28: 10, 1949.
18. Goldring, W. and Chasis, H. E. Hypertension and Hypertensive Disease, pp. 40–47. New York, 1944. The Commonwealth Fund Publisher.
19. Gladstone, S. A. Cardiac Output and Arterial Hypertension. New York, 1935. Privately printed.
20. Werkö, L. and Lagelöf, H. Studies on the circulation in man. IV. Cardiac output and blood pressure in the right auricle, right ventricle and pulmonary artery in patients with hypertensive cardiovascular disease. *Acta. med. Scandinav.*, 133: 427, 1949.
21. Varnauskas, E. Studies in hypertensive cardiovascular disease with special reference to cardiac function. *Scandinavian J. Clin. & Lab. Invest.*, 7: Suppl. 17, 1955.

# Bacterial Endocarditis Related to Cleaning and Filling of Teeth

## With Particular Reference to the Inadequacy of Present Day Knowledge and Practice of Antibiotic Prophylaxis for All Dental Procedures*

W. Proctor Harvey, M.D. *and* Maurice A. Capone, M.D.

Washington, D. C.

The causal relationship between dental extractions and bacterial endocarditis appears well documented clinically and has been stressed repeatedly.[1-16] Various studies indicate that from 10 to approximately 50 per cent of of cases of bacterial endocarditis are probably related to a dental focus of infection or previous dental extractions. It appears probable that in one of four or five cases a preceding dental extraction is related to subsequent bacterial endocarditis. It has therefore become generally accepted as sound medical practice to give patients with congenital or rheumatic valvular heart disease antibiotics (preferably penicillin) prophylactically prior to dental extractions. Also reported, but much less commonly stressed, are instances of bacterial endocarditis following various operative procedures, abortion, pregnancy with delivery and postpartum, infection, massage of infected prostates, tonsils or gums, and various diagnostic procedures including cystoscopy, bronchoscopy, sigmoidoscopy and others.[4,6,7] In addition there are occasional references to endocarditis apparently following dental procedures other than extraction, such as cleaning and/or filling of teeth. Favour et al.,[6] quoting from a large series of patients with subacute bacterial endocarditis, cited two specific cases in which there was a history of "teeth cleaned and filled" and another of "infected tooth filled" prior to the onset of their illnesses. It is of interest also that in the same report six additional cases were cited in which no specific dental procedures were performed, but the possible relation of poor dental hygiene such as "infected tooth," "gum infection" and "severe dental sepsis" was present. In separate reports, but citing the same two cases in each of their series, Palmer and Kempf[8] and Hopkins[9] observed two patients with rheumatic heart disease and bacterial endocarditis proven at autopsy, neither of whom had had dental extractions. One had "oral sepsis of a pyorrheal nature," and procaine hydrochloride was injected into the gums; another had "extensive repair work" in which several teeth were devitalized and filling of the root canals undertaken. Lichtman and Master[4] listed five of nineteen cases of subacute bacterial endocarditis following conditions other than operative or diagnostic procedures when endocarditis followed dental manipulation (no extraction). Ernstene[7] reported one case of bacterial endocarditis following bilateral periodontitis in his series of thirty-two in which the portal of entry was identified with reasonable certainty. Levine[11] states that "among the known specific precipitating causes of bacterial endocarditis, extraction of teeth or even simple cleaning is the most common. Such a history can be obtained in 20 per cent of the cases." Friedberg[12] also brings up the possibility.

In these references to bacterial endocarditis presumably following dental procedures other

* From the Department of Medicine, Georgetown University School of Medicine, Division of Cardiology, Georgetown University Hospital, Washington, D. C. This work was supported in part by grants from the U. S. Public Health Service, National Institutes of Health, Bethesda, Maryland (H-3319), Washington Heart Association, Special Cardiac Research Fund, and the Benjamin May Memorial Fund.

than extractions, there is little or no specific emphasis on the prophylactic use of antibiotics such as penicillin prior to these procedures. We have been impressed with the probable relation of cleaning and/or filling of teeth to bacterial endocarditis in view of the fact that in five patients admitted to our hospital over a period of twenty-two months, dental procedures, cleaning and filling of teeth (no extractions) appeared to be the precipitating cause of bacterial endocarditis.

## Case Reports

Case 1. A sixty-two year old man was hospitalized because of fever of one week's duration. He had known rheumatic heart disease with aortic stenosis. *Three weeks prior to admission, he had vigorous dental cleaning* which was followed in one week by intermittent chills and fever. Blood cultures taken before his admission were positive for Streptococcus viridans.

On admission he had a temperature of 102° F. and there were petechial lesions in the conjunctivae and buccal mucosa. Slight cardiomegaly with a grade 3 harsh aortic ejection systolic murmur were present. Despite treatment with penicillin and streptomycin a generalized petechial rash, an aortic diastolic murmur and a pericardial friction rub developed within a short period. Severe congestive heart failure progressed until his death on the ninth hospital day.

*Postmortem examination* revealed cardiac vegetations on a stenotic and calcific aortic valve with perforation of the right posterior cusp into the sinus of Valsalva, left and right atria and pericardial transverse sinus, resulting in pericardial tamponade.

Case 2. A twenty-nine year old man was admitted because of recurrent fever. Seven years prior to this admission he underwent successful surgery for coarctation of the aorta. *Two months prior to admission he had cleaning and filling of his teeth*, and subsequently noted continued recurrent fever. Blood cultures prior to admission grew out pure colonies of Streptococcus viridans.

Physical examination disclosed slight cardiomegaly with a grade 2 early blowing diastolic murmur heard along the left sternal border. A ventricular diastolic gallop was present and the tip of the spleen was palpable. Treatment consisted of penicillin for four weeks and recovery was uneventful. The *final diagnosis* was a Str. viridans endocarditis probably affecting a congenital bicuspid aortic valve.

Case 3. A sixty year old man with rheumatic heart disease and mitral insufficiency was admitted with a fever of undetermined origin of four months' duration. He had not had rheumatic fever, but was told fifteen years previously that he had a "heart murmur." *He had dental cleaning and filling* approximately one month before onset of his symptoms.

Physical examination was negative for abnormalities except for a grade 5 pansystolic murmur at the apex which was transmitted widely over the entire precordium. Blood cultures were positive for Str. viridans, and the patient was treated with penicillin and streptomycin for five weeks with an excellent recovery.

Case 4. A seventy-two year old woman was hospitalized because of fatigue, anorexia and diarrhea of several months' duration. She had known rheumatic heart disease with mitral insufficiency and chronic mild decomposition. She had *dental filling three months prior to admission*, shortly before the onset of her symptoms.

On physical examination she was febrile and a grade 4 harsh pansystolic murmur was heard at the apex. She had hepatosplenomegaly. Petechiae were noted in the conjunctivae of each eye. A diagnosis of bacterial endocarditis due to Str. viridans was established by repeated blood cultures. She received penicillin and streptomycin for six weeks with subsidence of fever and symptoms. However, her course was then complicated by a cerebrovascular accident with left hemiplegia, presumably secondary to an embolus from a healed vegetation. She died two years later after prolonged chronic illness and disabling hemiplegia.

Case 5. A twenty-three year old woman with rheumatic heart disease, mitral stenosis and insufficiency and aortic insufficiency was hospitalized because of chills, fever and arthralgia of three weeks' duration. For three years prior to admission she had been taking digitalis, diuretics and daily prophylactic penicillin. Three months prior to admission she discontinued taking the penicillin. Two months before admission she had "*dental filling*" and four to five weeks after this noted chills, fever, increasing dyspnea and generalized arthralgia.

Physical examination revealed a chronically ill, febrile young woman. There was a single Roth spot in her right eye and petechiae on the mucous membranes of her mouth. Osler nodes were noted in the hands with Janeway lesions in the hands and feet. The heart was enlarged to the left. The rhythm was regular with grade 2 systolic and diastolic murmurs at the base of the heart. At the apex there was a grade 4 pansystolic murmur and a grade 3 diastolic rumble with presystolic accentuation. The tip of the spleen was palpable.

Repeated blood cultures were negative, but despite this the diagnosis of bacterial endocarditis was made. Treatment with penicillin and streptomycin was instituted. The day after admission nuchal rigidity developed, and a polymorphonuclear pleocytosis was present in the spinal fluid. She became increasingly lethargic and died on her fifth hospital day.

TABLE 1
Knowledge of Cardiac Patients Concerning Need for Antibiotic Prophylaxis for Extractions vs. Cleaning and Filling of Teeth

| Type of Heart Disease | No. of Patients | Knowledge of Patient Concerning Prophylaxis for: | | | |
|---|---|---|---|---|---|
| | | Extractions | | Cleaning and Filling | |
| Rheumatic | 181 | 44 | 24.3% | 15 | 8.3% |
| Congenital | 55 | 9 | 16.4% | 4 | 7.3% |
| Functional vs. organic | 22 | 3 | 13.6% | 1 | 4.5% |
| Total | 258 | 56 | 21.7% | 20 | 7.7% |

*Necropsy* revealed bacterial endocarditis with vegetations along the edge of the deformed leaflets of the mitral valve and the chordae tendineae. She had a massive hemorrhage into the left lenticular nuclei and basal ganglia. A ruptured mycotic aneurysm with hemorrhage into the left cerebral hemisphere was also found.

## FURTHER CLINICAL STUDY

Over two years have now elapsed after this period of twenty-two months when these five patients were studied. We have continued to observe in our own hospital as well as in others, patients who have had bacterial endocarditis following dental procedures consisting of cleaning and/or filling of teeth; in addition, others have been seen following extractions alone or in combination with other dental manipulations.

In an effort to determine the adequacy of present day knowledge and the effectiveness of present methods of antibiotic prophylaxis (preferably penicillin), the following study was performed. A group of private patients seen in consultation, having a previous diagnosis of either rheumatic or congenital heart disease, were questioned by the same observer. Each was asked specifically concerning his previous instructions on dental prophylaxis for extractions, cleaning or filling. As shown in Table 1, a total of 258 patients were examined and questioned. Children under six years of age were excluded from the study. There were 116 men and 142 women. One hundred eighty-one had rheumatic valvular heart disease, fifty-five had congenital heart disease, and twenty-two had a previous diagnosis of either probable rheumatic or congenital heart disease but possibly fell into a functional category.

Those patients understanding that they should inform their dentists (1) of a heart lesion which might be susceptible to infection related to dental procedures and (2) that they had been instructed by their physicians to receive antibiotic prophylaxis, gave results as follows (Table 1): of 181 patients with rheumatic heart disease 44 (24.3 per cent) knew this concerning extraction of teeth, whereas only fifteen patients (8.3 per cent) were aware of this for cleaning and filling. Of the fifty-five patients with congenital heart disease, nine (16.4 per cent) understood about extractions, and only four (7.3 per cent) about cleaning and filling. Of twenty-two patients whose disease was classified as functional versus organic, three (13.6 per cent) knew of propylaxis with extractions, and one (4.5 per cent) with cleaning and filling. The total of 258 patients indicated that fifty-six (21.7 per cent) understood the precautions concerning extractions, and only twenty (7.7 per cent) those concerning cleaning and/or filling of teeth.

It was a surprising and important finding that only one of approximately five patients understood that they should tell their dentists they had rheumatic or congenital heart disease and had been instructed to receive antibiotic prophylaxis prior to dental extractions, and only one of thirteen patients understood this for cleaning and/or filling of teeth. The majority of these 258 patients had already had dental procedures, either extractions, cleaning, filling or a combination. As a result of this study it became evident that the relation of bacterial endocarditis to cleaning and filling of teeth has not been fully appreciated, and that it certainly has not been the usual practice for patients with valvular or congenital heart disease to receive antibiotic prophylaxis prior to cleaning and filling of teeth. It was also apparent that despite the generally accepted evidence relating dental extractions to bacterial endocarditis in such susceptible patients, prophylaxis in this group was performed only in the minority of patients.

## COMMENTS

*Bacteremia Following Dental Manipulations:* The relationship of bacterial endocarditis to dental procedures, particularly extractions, appears well established in patients with a valvular deformity from rheumatic heart disease or a congenital lesion such as a ventricular septal defect or patent ductus arteriosus. It has

also been well demonstrated that the Str. viridans[17–19] is the most common organism causing bacterial endocarditis and is a common inhabitant of the normal flora of the mouth. Strains of streptococci isolated in normal throats, extracted teeth, and in bacterial endocarditis have had the same distribution of serologic groups of Str. viridans.[5] Many studies have repeatedly shown the high incidence of bacteremia in dental extractions. Okell and Elliott[19] showed a transient bacteremia following extraction of teeth from obvious septic mouths in 75 per cent of the cases. In the patients showing no obvious gum disease extractions of teeth were followed by a transient streptococcal bacteremia in 34 per cent of the cases. Many studies have been performed showing a significant incidence of bacteremia following dental extractions,[17–25] which varies from 10 to 75 per cent. It has also been reported that a significantly high percentage of positive cultures may be obtained in dental procedures other than extractions.[26–29] For example, after rocking a single tooth with forceps, 86 per cent of twenty-one cases with "marked gum disease" and 25 per cent of twenty cases without detectable gum disease had positive blood cultures for streptococci following this manipulation.[22]

Cobe[23] reported positive cultures in 24 per cent of 305 cases after brushing of teeth, in 40 per cent after cleaning, in 17 per cent of 225 cases after chewing hard candy, and in none of 200 patients chewing gum. Murray[27] obtained positive blood cultures in 55 per cent of 336 patients with varying degrees of dental caries and pyorrhea after chewing a 1 inch cube of paraffin for a half hour. Round[28] reported on ten patients who chewed "mint lump" candy for ten minutes, blood cultures being taken before and afterwards. Two of five subjects showing pyorrheal disease showed bacteremia afterward, whereas five subjects without pyorrheal disease showed no bacteremia.

The exact interpretation of the accumulated data from these studies is a matter of debate. However, there appears to be ample evidence that various dental manipulations may be followed by bacteremia which may be a source for subsequent bacterial endocarditis. The efficacy of antibiotics in prevention of bacteremia following dental procedures appears established (penicillin being the drug of choice).[30–35] Further emphasis of this aspect does not seem warranted for the present discussion.

*Inadequacy of Present Day Knowledge Concerning Antiobiotic Prophylaxis:* From the case reports of our patients presented herein there appears to be a causal relationship not only between extraction of teeth, but also between cleaning and/or filling of teeth and subsequent bacterial endocarditis. It also appears obvious that in some way the necessary information concerning the importance of antibiotic prophylaxis prior to dental procedures (including cleaning and/or filling of teeth as well as extractions) represents a neglected aspect of treatment and prevention of heart disease. Where the fault lies is difficult to say. Perhaps physicians have not adequately educated patients as to the importance of remembering to tell their dentists that they have the type of heart disease that is subject to possible bacterial endocarditis. Certainly in a number of cases the patient has not received instructions by his physician. In some instances the patient may well have forgotten such instructions, and lastly, the dentist himself may not be aware of the importance of antibiotic prophylaxis. It is difficult for the dentist to appreciate this problem because of the duration between dental procedures and the onset of symptoms of bacterial endocarditis, which generally varies from weeks to months, thereby often obscuring the relationship. Despite the fact that the dental and also the medical literature, if carefully searched, suggests the relationship between the various dental manipulations (as already discussed) and subsequent bacterial endocarditis, it is also probable that the dentist himself, as well as the physician, has not appreciated the importance of antibiotic prophylaxis, particularly in reference to simpler procedures such as cleaning and/or filling of teeth and other manipulations that require rocking or abnormal motion of the teeth.

It is apparent that new efforts must be focused on adequate dissemination of this important prophylactic aspect to the physician, patient and dentist. In addition to the physician's role in giving specific instructions and educating the patient, it is suggested that the patient carry a card stating his specific cardiac lesion with specific recommendations for appropriate antibiotic therapy prior to all dental procedures. A screening history of every patient by the dentist should be routine. Only with such cooperation of the physician, patient and dentist can this aspect of prevention of heart disease be met effectively.

## Summary

Data are presented on five patients with bacterial endocarditis following dental procedures involving cleaning and/or filling of teeth (no extractions). Three patients subsequently died from complications. Str. viridans was cultured in four cases. Histories from 258 patients with rheumatic or congenital heart lesions revealed that only a minority was informed concerning the importance of prophylaxis prior to extractions, and in still fewer instances was there knowledge of its importance in relation to the cleaning and/or filling of teeth.

The importance of the role of close cooperation of the physician, patient and dentist is stressed as a necessity in prevention of this aspect of heart disease.



## Acknowledgment

Appreciation is expressed to Drs. Joseph Marilley and Michael McDonough for their assistance in this study.


## References


1. Cates J. E. and Christie, R. V. Subacute bacterial endocarditis. *Quarterley J. Med.*, 20: 93, 1951.
2. Anderson, D. G. and Keefer, C. S. The Therapeutic Value of Penicillin. Ann Arbor, Michigan, 1948. Edwards Bros.
3. Nelson, S. T. and White, P. D. Notes on 250 cases of subacute bacterial endocarditis studied and treated between 1927–1939. *Ann. Int. Med.*, 22: 40, 1945.
4. Lichtman, P. and Master, A. M. Incidence of valvular heart disease in people over fifty and penicillin prophylaxis of bacterial endocarditis. *New York J. Med.*, 49: 1693, 1949.
5. Selbie, F. R., Simon, R. D. and Robinson, R. H. Serological classification of viridans streptococcus from subacute bacterial endocarditis, teeth, and throat. *Brit. M. J.*, 49: 667, 1949.
6. Favour, C. B., Janeway, C. A., Gibson, J. G. and Levine, S. A. Progress in the treatment of sub acute bacterial endocarditis. *New England J. Med.*, 234: 71, 1946.
7. Ernstene, A. C., McGarvey, C. J. and Ecker, J. A. Prophylaxis of subacute bacterial endocarditis. *Cleveland Clinic Quart.*, 18: 1, 1951.
8. Palmer, H. R. and Kempf, M. Streptococcus viridans bacteremia following extraction of teeth; a case of multiple mycotic aneurysms in the pulmonary arteries. *J. A. M. A.*, 113: 1788, 1939.
9. Hopkins, J. A. Streptococcus viridans bacteremia following extractions of the teeth. *J. Am. Dent. A.*, 26: 2002, 1939.
10. Weiss, H. Relation of portals of entry in subacute bacterial endocarditis. *Arch. Int. Med.*, 64: 710, 1934.
11. Levine, S. A. Clinical Heart Disease, 5th ed., p. 211. Philadelphia, 1958. W. B. Saunders Co.
12. Friedberg, C. K. Diseases of the Heart, p. 804. Philadelphia, 1956. W. B. Saunders Co.
13. Pamphlet: Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections. New York. American Heart Association.
14. Pamphlet: How the Dentist Can Protect His Patients from Bacterial Endocarditis. New York, 1960. American Heart Association.
15. Garrod, L. P. Endocarditis and dental extraction. *Brit. M. J.*, 2: 727, 1953.
16. Brock, H. J. Treatment of recurrent subacute bacterial endocarditis by dental extraction. *New York J. Med.*, 52: 607, 1952.
17. Kraus, F. A., Casey, D. W. and Johnson, V. Classification of non-hemolytic streptococci recovered from bacteremia of dental origin. *J. Dent. Res.*, 32: 613, 1953.
18. Hayes, R. L. Clinical and bacteriological study of 340 pulp therapy cases. *J. Dent. Res.*, 22: 301, 1943.
19. Okell, C. C. and Elliott, S. D. Bacteremia and oral sepsis with special reference to aetiology of subacute endocarditis. *Lancet*, 4: 869, 1935.
20. Lazansky, J. P., Robinson, L. and Rodofsky, L. Factors influencing the incidence of bacteremias following surgical procedures in the oral cavity. *J. Dent. Res.*, 28: 533, 1949.
21. Burket, L. W. and Burn, C. G. Bacteremia following dental extraction: demonstration of source of bacteria by means of a new-pathogen (Serratia marcesens). *J. Dent. Res.*, 16: 521, 1937.
22. Elliott, S. D. Bacteremia and oral sepsis. *Proc. Roy. Soc. Med.*, 32: 747, 1939.
23. Cobe, W. Transient bacteremia. *J. Oral Surg.*, 7: 609, 1954.
24. McEntegart, M. D. and Porterfield, J. S. Bacteremia following dental extractions. *Lancet*, 2: 596, 1949.
25. Robinson, L., Kraus, F. W., Lazansky, J. P., Wheeler, R. E., Gordan, S. and Johnson, W. Bacteremia of dental origin. *J. Oral Surg.*, 3: 519, 923, 1950.
26. Richards, J. H. Bacteremia following irritation of foci of infection. *J. A. M. A.*, 99: 1496, 1932.
27. Murray, M. and Moosnick, F. Incidence of bacteremia in patients with dental disease. *J. Lab. & Clin. Med.*, 26: 801, 1941.
28. Round, H., Kirkpatrick, H. J. R. and Hails, C. G. Further investigations on bacteriological infections of the mouth. *Proc. Roy. Soc. Med.*, 29: 1552, 1936.
29. Ostrander, F. D. and Crowley, M. C. The effectiveness of clinical treatment of pulp-involved teeth as determined by bacteriological methods. *J. Endodontia*, 3: 6, 1948.
30. Hirsh, H. L., Vivino, J. J., Merril, A. and Dowling, H. F. Effect of prophylactically administered penicillin on incidence of bacteremia following extractions of teeth. *Arch. Int. Med.*, 8: 868, 1948.
31. Rhoads, P. S., Schram, W. R. and Adair, D. Bacteremia following tooth extraction. Prevention with penicillin and NU 445. *J. Am. Dent. A.*, 41: 55, 1950.
32. Bender, I. B. and Pressman, R. S. Antibiotic

treatment of the gingival sulcus in prevention of post-extraction bacteremia. *J. Oral Surg.*, 14: 20, 1956.

33. GLASER, R. J., DANKNER, A., MATHES, S. B. and HARFORD, C. G. Effect of penicillin on the bacteremia following dental extraction. *Am. J. Med.*, 4: 55, 1948.
34. NORTHROP, P. M. and CROWLEY, M. C. The prophylactic use of sulfathiazole in transient bacteremia following the extraction of teeth. A preliminary report. *J. Oral Surg.*, 1: 19, 1943.
35. NORTHROP, P. M. and CROWLEY, M. C. P. Further studies on the effect of the prophylactic use of sulfathiazole and sulfamerazine on bacteremia following extraction of teeth. *J. Oral. Surg.*, 2: 134, 1944.

# Intermittent Ventricular Parasystole with Observations on Its Relationship to Extrasystolic Bigeminy*

LEO SCHAMROTH,† M.B., B.CH. (RAND) *and* HENRY J. L. MARRIOTT, M.D.

Baltimore, Maryland

THE RELATIONSHIP between extrasystolic and parasystolic impulse formation is unclear. When parasystole is intermittent, in all cases reported to date, each run of parasystolic rhythm has been initiated by a coupled extrasystole.[1–6] Conversely, the same ectopic center that gives rise to a parasystolic rhythm can at times produce extrasystoles. Thus, Scherf and Schott[7] described a case with simple parasystole which some months later showed only extrasystolic rhythm from the same ectopic focus. The actual transition from parasystolic to extrasystolic rhythm, however, has rarely been observed and we have been able to find only three examples. The case of Vedoya and Battini[8] showed a fast ventricular parasystolic rhythm which at one stage terminated in an extrasystole from the same focus and the following day showed extrasystoles only. A report by Scherf and others[5] showed spontaneous intermittent parasystole which on one occasion terminated in extrasystolic ventricular bigeminy (their Case 1). Schamroth's[6] case showed extrasystolic ventricular bigeminy which was abolished by eyeball compression. Sinus rhythm ensued for one and one-half minutes and was followed by bursts of intermittent parasystole from the same ectopic focus. After four minutes, the rhythm reverted once again to extrasystolic ventricular bigeminy.

We have observed two cases of digitalis intoxication in which there is clear evidence of alternate extrasystolic and parasystolic impulse formation from the same ectopic focus, transitions back and forth between the two rhythms being seen repeatedly. In the course of analyzing our tracings several additional features were noted which have a bearing on the problems of ectopic impulse formation.

## CASE REPORTS

CASE 1. Figure 1 is part of an electrocardiogram recorded from a fifty-seven year old Negro man with hypertension during a period of digitalis intoxication. The basic sinus rhythm is interspersed with ectopic beats (numbered 1 to 11). These ectopic beats are all of identical contour, except complex 10 which is intermediate in configuration between that of the sinus and ectopic beats and is a fusion beat. At first inspection beats 1 to 3 appear to be extrasystoles occurring every seventh beat. However, the interectopic intervals between complexes 1 to 5, and 8 to 11, are all multiples or near multiples of 150‡ and these ectopic beats also show variations in their coupling intervals to the preceding sinus beats ("parasystolic beats," Fig. 2). The presence of variable coupling, interectopic intervals with a common denominator and fusion beats indicates a parasystolic rhythm. Beats 5 to 8 show relatively constant coupling and their interectopic intervals, therefore, measure about 138 or approximately double the sinus cycle length; this indicates that beats 6 to 8 are true extrasystoles. These beats also show retrograde conduction to the atria accounting for the earlier and abnormal P waves seen just after the ectopic QRS complexes. The coupling intervals of these beats are 43, 43 and 47 respectively. Invariably the coupling interval of the beat terminating parasystole and heralding a bigeminal run (e.g., beat 5 in Fig. 1) is the shortest ("beats terminating parasystole," Fig. 2) and that of the beat that ends such a run (e.g., beat 8 of Fig. 1) is the longest ("terminal extrasystoles," Fig. 2). Between these extremes the coupling intervals of the extrasystolic rhythm vary only within narrow limits ("extrasystoles," Fig. 2). These beats therefore ap-

‡ All time intervals are expressed in hundredths of a second.

* From the Departments of Medicine, Mercy and University Hospitals, Baltimore, Maryland.
† Present address: Johannesburg, South Africa.

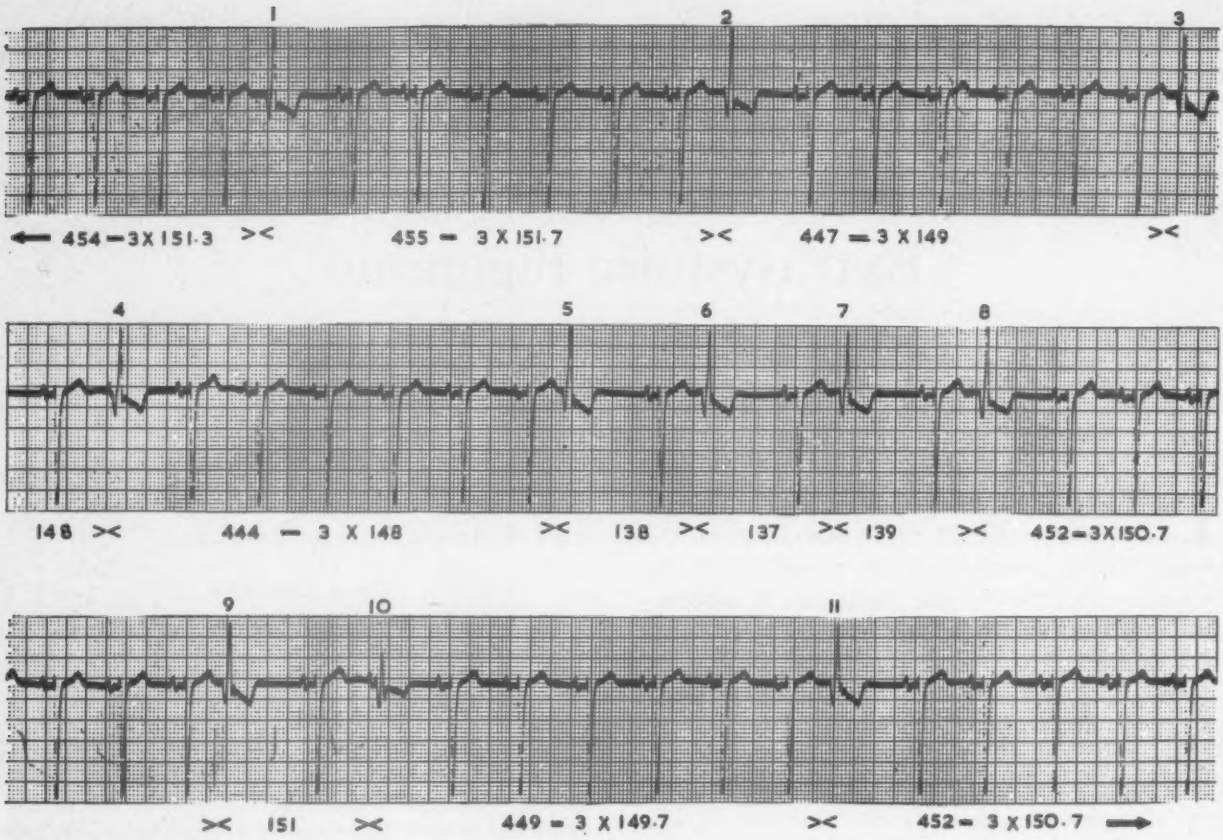



FIG. 1. Case 1. Continuous strip of lead I showing parasystole (ectopic beats 1 to 5) changing to extrasystolic ventricular bigeminy (ectopic beats 6 to 8) and reverting once again to parasystole (ectopic beats 8 to 11). Full description in text.

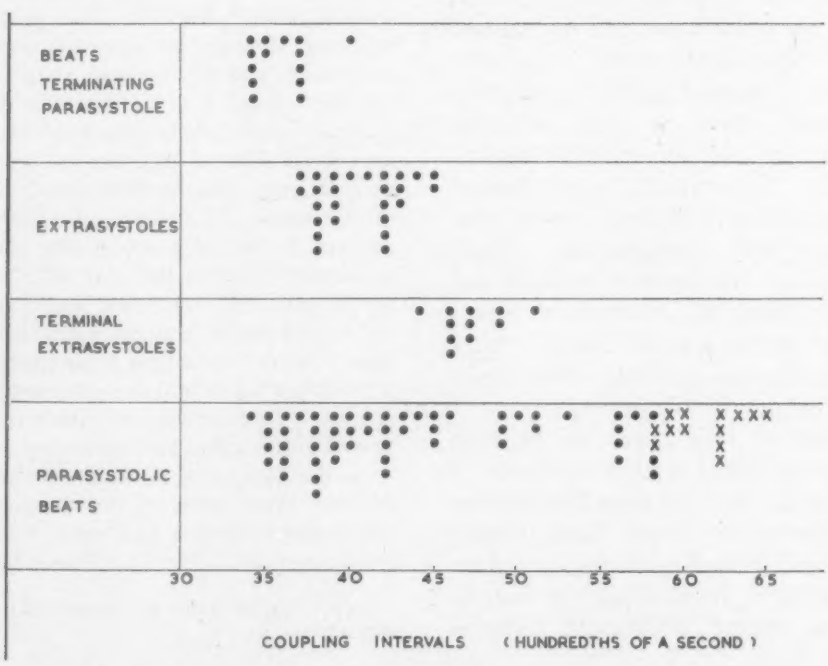



FIG. 2. Graphic display of all the coupling intervals of the first recording of Case 1 (cf. Fig. 1). X = coupling interval terminated by fusion beat.

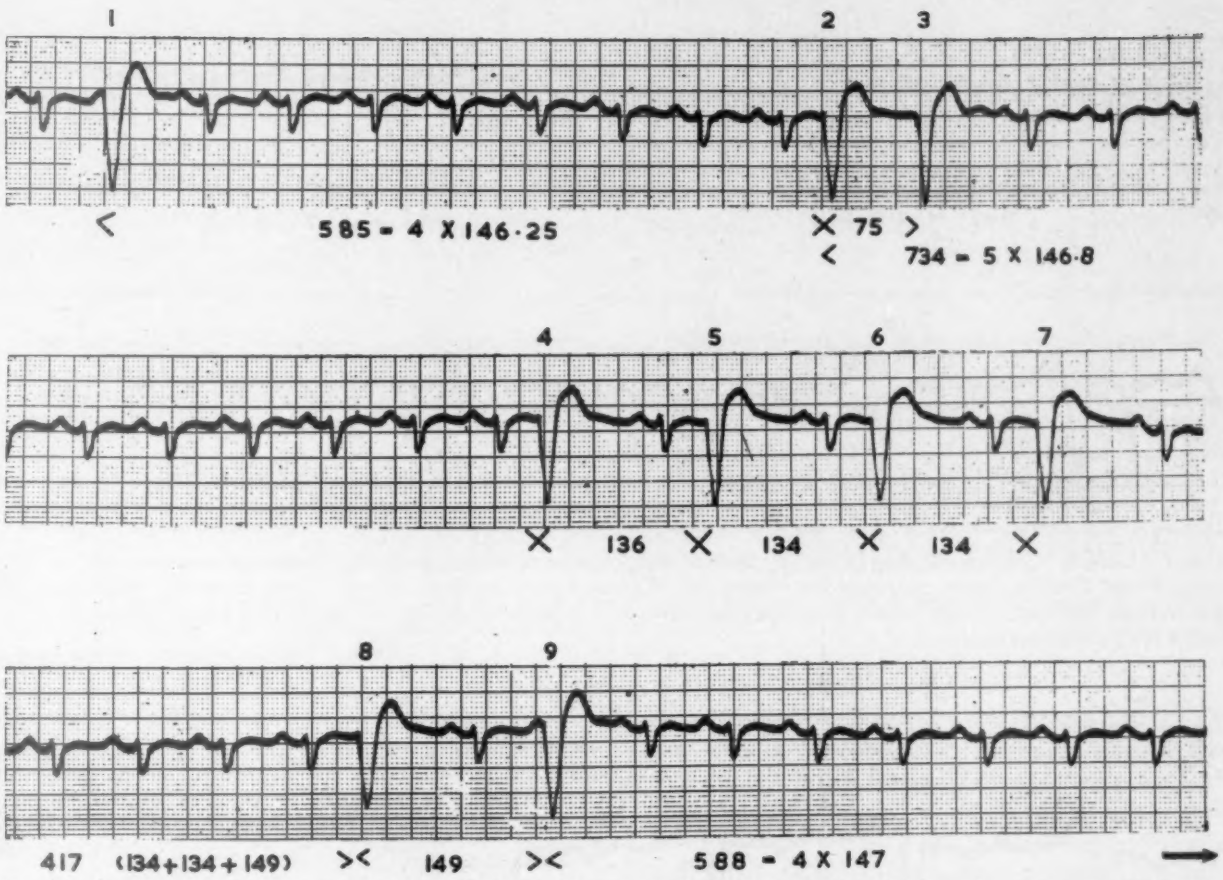



FIG. 3. Case 2. Continuous strip of lead II showing parasystole (ectopic beats 1 to 4) changing to extrasystolic ventricular bigeminy (ectopic beats 5 to 7) and reverting once again to parasystole (ectopic beats 8 and 9). *Concealed extrasystoles* are inferred during the interval between ectopic beats 7 and 8 (full argument in text).

pear to be true extrasystoles and this tracing demonstrates the presence in one recording of parasystole (automatic beats) and extrasystoles (forced beats). The parasystolic rhythm always begins with a forced beat or extrasystole; the ectopic focus then assumes the property of automatic impulse formation and the rhythm changes to parasystole.

This intermittent parasystole could be demonstrated many times during the recording as the rhythm alternated between extrasystolic bigeminy and parasystole. An analysis of all the interectopic intervals during this six minute recording showed that they could be divided into two main groups as follows:

A. Seventy-three interectopic intervals that were multiples of 150 (mean 150.35, range 144.1 to 155.5 but with close grouping around the mean). These represent parasystolic rhythm.

B. Forty-one interectopic intervals that were multiples of 136 (mean 136.3, range 133 to 137). These intervals approximate double the sinus cycle length and represent episodes of extrasystolic rhythm. Transition between the two rhythms was occasionally marked by an intermediate interectopic interval of about 140.

CASE 2. Figure 3 is part of an electrocardiogram recorded during a period of digitalis intoxication in a fifty-eight year old white man with coronary artery disease. Sinus rhythm with first degree A-V block is interrupted by ectopic beats (numbered 1 to 9). Beats 5, 6 and 7 show fixed coupling of 41 to the preceding sinus beats, constituting a run of extrasystolic bigeminy. The anomalous beat heralding this run (beat 4) is coupled to the preceding sinus beat by a shorter interval of 39. All the other anomalous beats show variable coupling and their interectopic intervals are indicated in Figure 3. As these intervals are all multiples or near multiples of 149, and the coupling intervals vary, a parasystolic rhythm can be presumed. In the record, other parasystolic interectopic intervals (not shown) ranged from 146.4 to 151. This tracing, therefore, contains both parasystole and extrasystoles.

The ectopic cycle length between complexes 2 and 3 is 75; i.e., approximately half the interectopic interval of 149. From this one may presume the existence of a 2:1 exit block of the parasystolic discharge which was temporarily dissipated after complex 2, momentarily allowing 1:1 conduction.

All the interectopic intervals in this two minute tracing are accurately divisible by either the extrasystolic interectopic interval of 136 (135.5 ± 1.5)

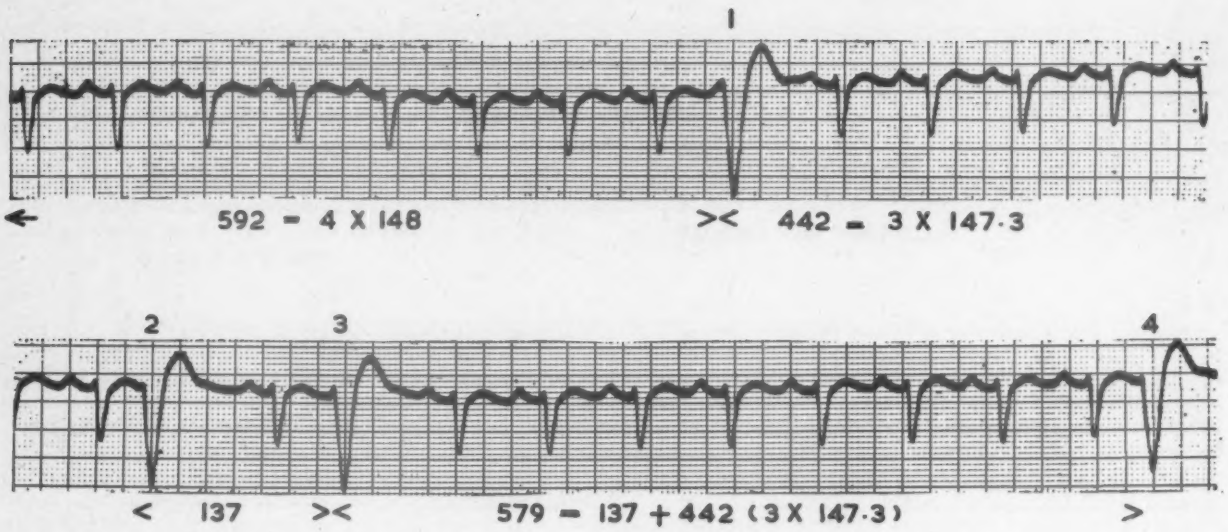



FIG. 4. Case 2. Continuous strip of lead II (later section of same recording as in Fig. 3) showing parasystole (ectopic beats 1 and 2) changing to extrasystolic ventricular bigeminy (ectopic beats 2 and 3) and reverting once again to parasystolic rhythm (ectopic beat 4). A *concealed extrasystole* is inferred during the interval between ectopic beats 3 and 4 (full argument in text).

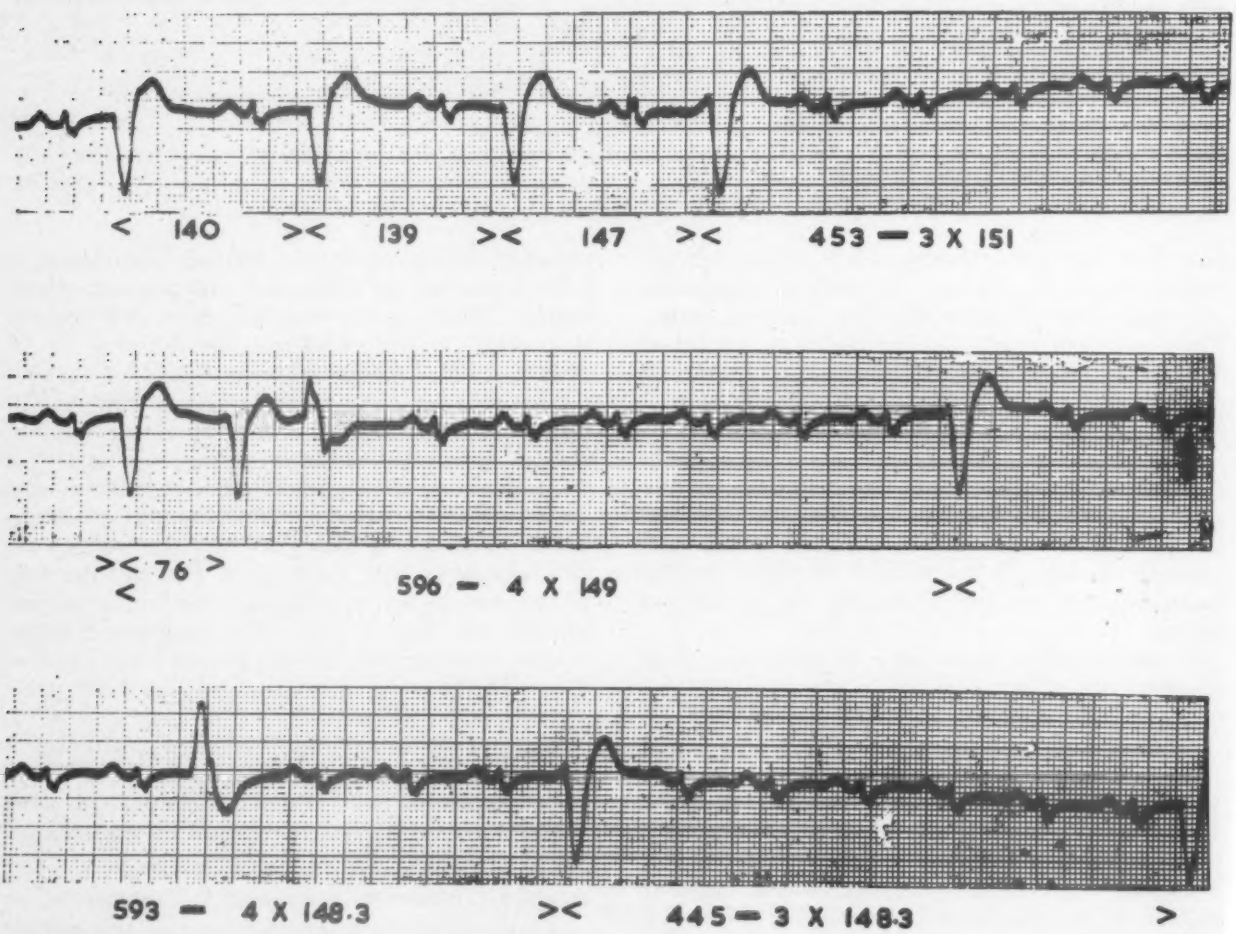



FIG. 5. Case 2. Continuous strip of lead II showing extrasystolic rhythm (the first three anomalous complexes) changing to parasystolic rhythm with average interectopic interval of 149 hundredths of a second (full description in text).

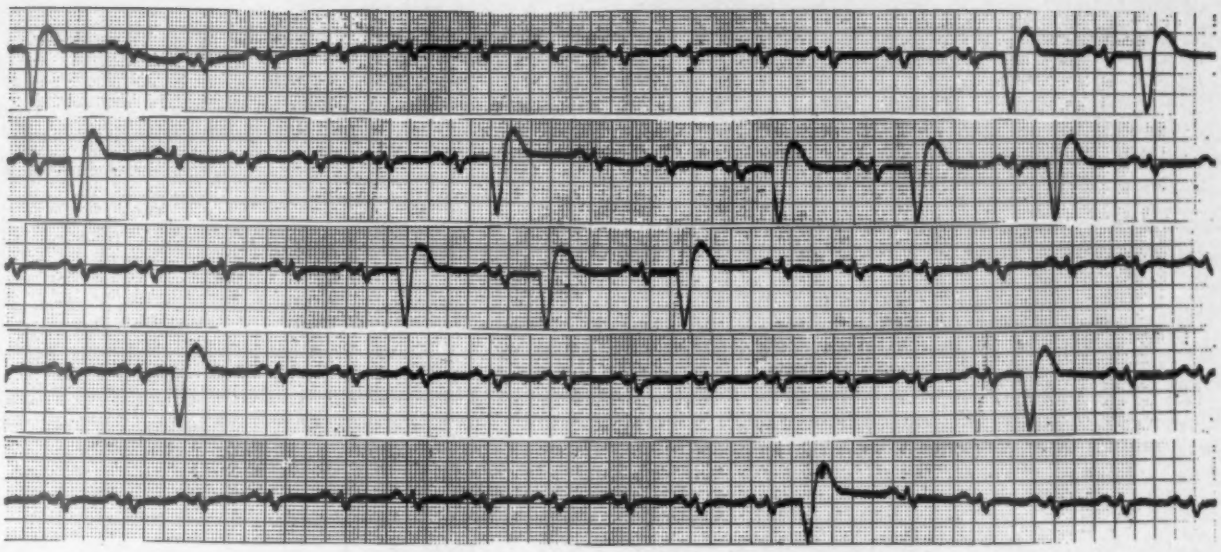


FIG. 6. Case 2. Continuous strip of lead II. A section of a four minute recording illustrating *concealed extrasystolic ventricular bigeminy*. Note that only odd numbers of sinus beats (13, 1, 1, 5, 3, 1, 1, 7, 1, 1, 4, 11, 13) occur during the interectopic intervals (cf. Table II).

or the parasystolic interval of 149 (148.7 ± 2.3), with two exceptions: these are the interval between beats 7 and 8 (Fig. 3) which measures 417 and that between beats 3 and 4 (Fig. 4) which measures 579. Neither of these figures is divisible by either 149 or 136. Further analysis, however, discloses that 417 may be "broken down" to 134 + 134 + 149, and 579 to 137 + 442 (3 × 147.3). Thus, one is tempted to assume that these intervals are composed of a combination of extrasystolic and parasystolic intervals. If this is so, the discharge of the extrasystoles is not electrocardiographically manifest and they may well be called *concealed extrasystoles;* and in these two instances the parasystolic rhythm "takes off" from a concealed extrasystole.

Figure 5 was recorded ten days later during another period of digitalis intoxication. This recording likewise shows extrasystolic rhythm (the first three anomalous complexes) which changes to parasystolic rhythm with an average interectopic interval of 149. Evidence of a dissipation of a 2:1 exit block is again noted at the beginning of the second strip. Occasional ectopic beats from a different focus are noted (third ectopic beat in second strip and first ectopic beat in bottom strip). These do not interfere with the parasystolic rhythm.

It was noteworthy that during the interval between the two periods of digitalis intoxication, when digitalis effect was much diminished, the parasystolic rhythm virtually disappeared and the sinus rhythm was interrupted mainly by extrasystolic beats (Fig. 6).

## COMMENTS

### INTERMITTENT PARASYSTOLE

Following the classic descriptions of parasystole by Kaufman and Rothberger,[9,10] Scherf[11] in 1926 produced a parasystolic rhythm in the dog by means of induction shocks. The rhythm was shortlived but could be repeatedly elicited; sinus rhythm prevailed between the artificially induced runs of parasystole. Scherf[11] first suggested the term *intermittent parasystole* and similar observations were later repeated.[12,13]

Clinical examples of intermittent parasystole are rare. Scherf and Boyd[1] described two cases (their Cases 2 and 3) in which there was "a periodic awakening and vanishing of an active ventricular center, . . .not disturbed by the sinus stimuli." Further examples of intermittent parasystole were reported by Mueller and Baron;[2] Langendorf and Pick[3] (their Figs. 3 and 4); Katz and Pick[4] (their Fig. 63); Scherf and others[5] and Schamroth[6] (his Fig. 10).

A rare kindred arrhythmia manifests a progressive lengthening in the coupling intervals of ectopic beats until one ectopic beat is "dropped" and the cycle may then repeat itself. There are several variants of this but one is here concerned only with that form in which the *interectopic intervals are constant.* Such progressive increase in the coupling intervals may be due to an increasing exit block of the Wenckebach type from the ectopic center or to a similar phenomenon in the "re-entry" pathway—if one subscribes to the re-entry theory of extrasystoles. It seems unlikely, however, that the increment per beat should always be precisely the amount that keeps the interectopic intervals constant. A parasystolic mechanism with an ectopic discharge rate slightly slower than

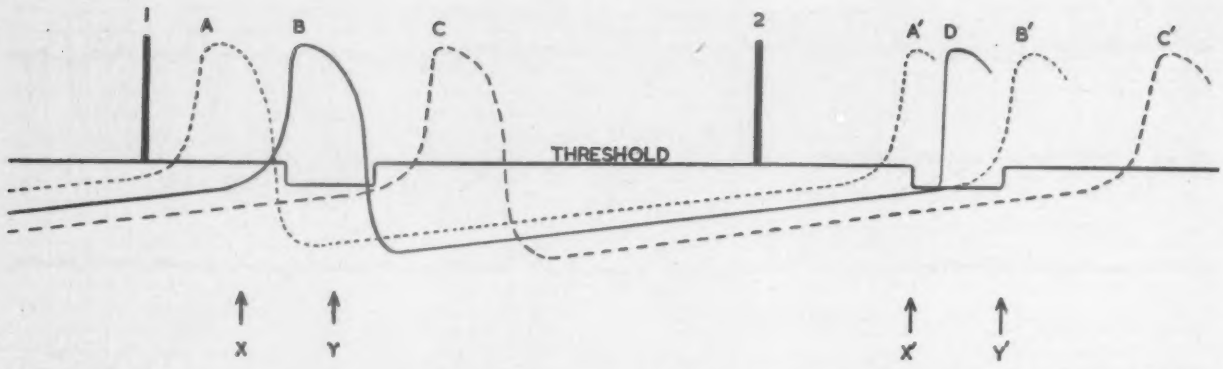



FIG. 7. Diagrammatic representation of the action potentials of the ectopic discharges and the effect of their time relationship to the sinus impulse (full description in text). For clarity, the action potentials of the sinus beats have not been graphed but are represented by the vertical bars 1 and 2.

double the sinus cycle would seem to be a more likely explanation. A beat may fail to appear either because of spontaneous intermittence of the parasystolic discharge, or because the discharge eventually falls within the refractory period of a sinus beat, an occurrence which is sometimes associated with the termination of the parasystole. If the long interectopic interval following such a "dropped beat" is not an exact multiple of the other interectopic intervals, an intermittent parasystole may be assumed. Examples of this arrhythmia may be seen in tracings published by Zander[14] and by Scherf and Schott[15] (their Fig. 130); another possible example may be seen in a record published by Mack and Langendorf.[16]

*The criteria for the diagnosis of intermittent parasystole* may be outlined as follows:

1. The ectopic rhythm must possess two inherent characteristics of parasystole: there must be a rhythmic ectopic discharge and protection of the ectopic center. This will result electrocardiographically in (A) interectopic intervals that are multiples of a common denominator; (B) variation in the coupling intervals with the possibility of fusion beats.

2. The onset and termination of the parasystolic rhythm must be observed. As an interruption in parasystolic rhythm may be due either to true intermittence or to exit block simulating intermittence, all such interruptions should be scrutinized to rule out exit block; i.e., the interectopic interval between the termination of the parasystolic rhythm and its resumption must *not* be a multiple of the common interectopic interval.

These criteria could be rigidly applied to our cases in both of which the onset and termination of parasystolic rhythm were repeatedly observed.

### THE PROTECTIVE MECHANISM

The nature of the protective mechanism in parasytole is one of the principle enigmas of cardiac physiology. It has long been envisaged as a spherical zone of unidirectional block surrounding the ectopic center,[9] hence the term "protective block." Varying degrees of refractoriness in the surrounding tissues have been postulated to account for both the entrance and exit blocks.[17] While conceding that a zone of refractoriness may exist in some cases, Scherf and Schott[18] have suggested that the protective mechanism may be explained by the strength of the dominant impulse relative to the excitability of the ectopic center. Thus, if the impulses from the dominant center are not of sufficient strength to stimulate the ectopic center and/or the ectopic center itself is less excitable, this in itself would be sufficient to protect the ectopic center. Scherf and Schott[18] thus proposed that the abstract term "protection" be substituted for protective block.

It is also obvious that if the ectopic center discharges at a faster rate than the sinus pacemaker, the refractoriness following such a rapid discharge in itself will be sufficient to protect the ectopic pacemaker. It is not definite whether this form of protection should qualify as a constituent of the parasystolic mechanism; if it should, then most paroxysms of tachycardia are examples of intermittent parasystole. But surely it is the nature of the protection, a protection which is not dependent upon rate, that should be considered as the essence of the parasystolic mechanism. Parasystolic rhythms with

faster ectopic pacemakers can exist but in such cases it must be clearly demonstrated that there is a protective mechanism apart from that due to the rapid discharge. In the case of Vedoya and Battini[5] the parasystolic rate was faster than the sinus rate, but the interval between the apparent termination of the fast parasystolic rhythm and the beginning of another "paroxysm" was always a multiple of the length of the ectopic cycle. In other words, the apparent cessation of the parasystolic rhythm was due to an exit block and the ectopic rhythm continued unseen but protected from the sinus impulses. A protective mechanism thus existed apart from that due to the fast rate of discharge.

### THE ONSET OF PARASYSTOLIC RHYTHM

In all previous records,[1–6] intermittent parasystole has been initiated from a typical extrasystole; i.e., a forced beat with fixed coupling. In both our cases, the parasystolic rhythm was always preceded by a run of bigeminal rhythm and, therefore, always began from the last coupled beat of such a run; this terminal extrasystole was invariably characterized by a longer coupling interval than preceding couplets. In two exceptional instances in Case 2, calculation suggested that the terminal extrasystole which initiated the parasystolic run was concealed; i.e., its discharge occurred intrinsically but was not electrocardiographically apparent; a *concealed extrasystole.*

### THE TERMINATION OF PARASYSTOLIC RHYTHM

Parasystolic rhythm may terminate because the inherent rhythmicity of the ectopic center ceases spontaneously, or because the protection of the ectopic center is dissipated. In our cases the termination of parasystolic rhythm was unique for it occurred *only* when the parasystolic impulse fell within a certain vulnerable range following the sinus impulse. This observed fact tempts one into theoretic paths in search of an explanation and makes it desirable to outline certain of the electrical phenomena of automatic centers and to recapitulate the current concepts of extrasystolic impulse formation.

Nonpacemaking cells have a stable resting potential; i.e., a constant subthreshold level which remains "horizontal" until depolarization results in an abrupt reversal, the action potential. In contrast, centers having the property of spontaneous rhythmicity have an unstable resting potential which exhibits a gradually rising "slope" of slow depolarization until the level of instability, the threshold potential, is reached[19–22] (Fig. 7).

*Enhancing Effects Following a Sinus Beat:* The prevailing concepts of extrasystolic impulse formation, *the re-entry theory* and *the theory of ectopic genesis,* both assume that the extrasystole is in some way dependent upon or precipitated by the preceding sinus beat. The re-entry theory postulates a localized area of refractoriness in the pathway of the sinus impulse which, after depolarizing the surrounding tissues, approaches and re-enters the refractory area from another direction. The refractory area has meanwhile become excitable again and is thus able to propagate the re-entering impulse so that an extrasystole results. Apart from the many cogent reasons already advanced against this theory,[23] its application to intermittent parasystole is unsatisfactory because it would assume one mechanism, re-entry, for the first extrasystole and another mechanism for the subsequently acquired automaticity and protection. Furthermore, we can see no application of the re-entry theory to the manner of termination in our cases, whereas the theory of ectopic genesis adequately explains all the observed phenomena. This theory assumes that the extrasystole is generated as a result of some enhancing effect of the preceding sinus impulse. There are several enhancing mechanisms which could play a role. The *supernormal phase* of the sinus beat could conceivably enhance a subthreshold ectopic focus. While this mechanism may play a part in the genesis of some extrasystoles, its application to the majority is unsatisfactory[24] because its excitability potentiation is relatively small and its duration is too short to explain some extrasystoles with relatively long coupling intervals.

A more likely enhancing mechanism may be the *Wedensky effect.* Wedensky[25] showed that a subthreshold stimulus which produced *no* response could, when applied after a maximal induction shock, elicit a response. This enhancing effect lasts longer than the supernormal phase. The sinus or initiating beat is likened to the induction shock which enables a previously subthreshold ectopic focus to become threshold and elicit a response, the extrasystole. This effect may be related to oscillatory negative after-potentials following a propagated impulse.[26] These after-potentials may enhance the excitability of a subthreshold focus and result in another propagated impulse. Wedensky[27]

TABLE I
Case 1. Analysis of Sinus Cycle Lengths (in hundredths of a second)

| During Extrasystolic Rhythm | During Parasystolic Rhythm | |
|---|---|---|
| 70 | 66 | 65 |
| 70 | 67 | 65 |
| 68 | 65 | 64 |
| 68 | 65 | 65 |
| 72 | 65 | 65 |
| 69 | 65 | 64 |
| 68 | 66 | 64 |
| 68 | 66 | 64 |
| 67 | 65 | 63 |
| 67 | 65 | 67 |
| 67 | 65 | 64 |
| 67 | 67 | 65 |
| 67 | 65 | 65 |
| 68 | 65 | |
| 69 | 64 | |
| 67 | 64 | |
| 70 | 64 | |
| 70 | 64 | |
| 68 | 64 | |
| 68 | 65 | |
| Mean 68.4 | 65.1 | |
| Range 67 to 70 | 63 to 67 | |

also showed that an impulse arriving at a blocked zone enhanced the excitability *beyond* the block—*Wedensky facilitation.* Thus, if there is some local impediment in the conduction of the sinus impulse to the ectopic focus, the threshold of the ectopic focus is lowered and its excitability enhanced so that it may then initiate it own impulse, the extrasystole.

In both our cases, termination of parasystole occurred *only* when the parasystolic discharge fell within a certain narrow range shortly after a sinus beat. When the discharge fell within this range, extrasystolic rhythm usually ensued although parasystolic rhythm occasionally continued; but when the discharge fell outside this range, parasystolic rhythm *always* continued. This suggested that spontaneous cessation of rhythmicity was most unlikely and that termination was critically related to the timing of the parasystolic discharge in relation to the sinus impulse. It would thus seem that the first extrasystole following the parasystolic run (e.g., beat 6 in Fig. 1; diagrammatically illustrated as D in Fig. 7) was in some way linked with the end of the parasystolic rhythm.

*To recapitulate the physiologic concepts so far considered:*

1. Protection is thought to be due to lowered excitability of the ectopic center relative to the sinus impulse.
2. Pacemaker activity is characterized by an unstable resting potential revealed by a slope of slow depolarization which gradually approaches threshold level.
3. The enhancing effect following a sinus beat is due to a temporary lowering of threshold.

*Effect of Time Relationship of Ectopic Discharges to the Sinus Impulse:* Applying these concepts to the termination of parasystole in our cases the following may be postulated: The resting potential of the parasystolic center is relatively inexcitable and remains subthreshold to impulses from the dominant center. This serves as a protective mechanism. The "resting potential" of the parasystolic center, however, exhibits a gradual upward slope of depolarization towards the threshold level. The terminal, near threshold, part of the slope could be influenced by the sinus impulse if it falls within the enhancing effect of the preceding sinus beat. The enhancing effect temporarily lowers the threshold and can be represented as a "trough" (Fig. 7). If the terminal part of the slope enters this enhancing "trough," the parasystolic discharge may be prematurely precipitated; i.e., the beat is forced and the automatic impulse is converted into a coupled extrasystole. If the parasystolic discharge falls at position B (Fig. 7), the next anticipated parasystolic discharge would occur at position B′. However, the terminal slope of the resting potential encounters the enhancing effect of the sinus beat, the "trough" of lowered threshold, and the parasystolic discharge is thus prematurely precipitated at D. If the parasystolic discharge falls earlier (e.g., at A), or later (e.g., at C), the subsequent resting potential slopes do not enter the enhancing trough of lowered threshold and consequently their discharges occur at the anticipated positions (A′ and C′), i.e., they are not prematurely discharged. It will be seen that the vulnerable position for the termination of a parasystolic run will be a narrow range around position B, namely X to Y, which corresponds to the duration of the enhancing through X′ to Y′. If this hypothesis is correct, the ectopic rhythm, once it has entered the sphere of influence of the sinus beat, becomes semi-automatic or "parasystoloid"; the center continues to build up regular impulses but these for a time are prematurely forced by the enhancing influence of the sinus beats.

OBSERVATIONS DURING EXTRASYSTOLIC AND PARASYSTOLIC RHYTHMS

Analysis of the sinus cycle lengths in Case 1 shows that those cycles found between the longer interectopic intervals during extrasystolic rhythm ranged from 67 to 70 with a mean of 68.4, whereas those during parasystolic rhythm ranged from 63 to 67 with a mean of 65.1 (Table I). This small but distinct difference remains unexplained and we have been unable to find a previous similar observation.

It was noted that the parasystolic and sinus discharge rates remained relatively constant during the stage of digitalis intoxication, being approximately 149 and 67 respectively in both cases. In Case 1, however, with lessening digitalis effect five days later, slowing of the parasystolic discharge to a cycle length of about 172 and a concomitant lengthening of the sinus cycle to 75 were observed. A similar parallel slowing of both pacemakers was noted by Scherf and Schott.[7]

*Concealed Bigeminy:* The most remarkable feature of all, which may perhaps forge a further link between bigeminal extrasystolic rhythm and parasystole, was the observed fact that, whenever runs of bigeminal extrasystolic rhythm were interrupted by runs of sinus rhythm, a situation that occurred on numerous occasions in both cases, there was always, without exception, an *odd* number of intervening sinus beats (Fig. 6). Similarly, in a third case which manifested only intermittent extrasystolic bigeminy and no runs of parasystole, only *odd* numbers of sinus beats were observed between the ectopic beats during a continuous recording of twenty minutes (Table II). In other words, in these three cases, whenever bigeminal extrasystolic rhythm was interrupted, *it was always resumed with an extrasystole coupled to a sinus beat to which an extrasystole would have been coupled if the bigeminy had continued uninterrupted.* This compels the assumption that the bigeminal tendency was persistent though invisible and that the extrasystolic focus was regularly discharged, but that depolarization remained localized so that the surrounding myocardium was not invaded and no complex was written on the electrocardiogram. This hypothesis lends further weight to our earlier postulate of concealed extrasystoles, the concept being here extended to *concealed bigeminy*. Why some extrasystolic discharges should remain localized is problematical but the assumption is in harmony with the accepted views of exit block as applied to pacemakers such as the S-A node (e.g., 2:1 S-A block) and parasystolic centers. Furthermore, just as protection is not necessarily due to block but may be due to a disproportion between intensity of stimulus and excitability of focus, so the inability of the ectopic impulse to invade the surrounding myocardium could be due to a similar disproportion between intensity of stimulus and excitability of the myocardium, rather than to exit block as at present understood.

TABLE II

Number of Sinus Beats Occupying Interectopic Intervals During Extrasystolic Rhythm

| Number of Sinus Beats | Frequency | | |
|---|---|---|---|
| | Case 1 | Case 2 | Case 3 |
| 1 | 43 | 19 | 172 |
| 2 | 0 | 0 | 0 |
| 3 | 3 | 3 | 71 |
| 4 | 0 | 0 | 0 |
| 5 | 4 | 5 | 9 |
| 6 | 0 | 0 | 0 |
| 7 | 3 | 6 | 8 |
| 8 | 0 | 0 | 0 |
| 9 | 3 | 5 | 3 |
| 10 | 0 | 0 | 0 |
| 11 | 1 | 4 | 2 |
| 12 | 0 | 0 | 0 |
| 13 | 0 | 2 | 2 |
| 17 | 1 | ... | 2 |
| 21 | ... | ... | 2 |
| 23 | ... | ... | 1 |
| 25 | ... | ... | 1 |
| 27 | ... | 1 | ... |
| 37 | ... | ... | 1 |
| 39 | ... | ... | 1 |
| 41 | ... | ... | 1 |
| 51 | ... | ... | 1 |
| 61 | ... | 1 | ... |
| 65 | ... | ... | 1 |
| 97 | ... | ... | 1 |
| Period of observation (minutes) | 6 | 4 | 20 |

*Relation Between Ventricular Bigeminy and Parasystole:* Kaufman and Rothberger[28] originally postulated that ventricular extrasystolic bigeminy was parasystolic, but this tenet was properly dismissed[29,30] because it was based on the constant interectopic interval which, of course, was simply a function of regular sinus rhythm with constancy of coupling leading inevitably to constant interectopic intervals also. Our observation, however, suggests that some forms of ventricular extrasystolic bigeminy

may at times be peculiarly related to parasystole; and it is tempting to wonder if the form of bigeminy just described is not a special extrasystolic variant with inherent parasystolic tendencies. From the observations here presented, it appears likely that in certain circumstances, perhaps especially under the influence of digitalis, some forms of bigeminy may after all represent at least a stepping-stone to parasystole.

## Summary

1. Two cases of intermittent parasystole are described in which there is alternate extrasystolic and parasystolic impulse formation from the same focus; transitions between the two rhythms are repeatedly observed.

2. It seems that intermittence results when the parasystolic focus is subjected to the enhancing effect of the sinus discharge whereby the automatic beat is prematurely precipitated, thus becoming a forced beat.

3. This phenomenon can be explained on the basis of a property of automatic centers; namely, that their resting potentials exhibit a gradual upward "slope" of depolarization. With critical timing, the terminal part of the "slope" (i.e. its near threshold level) may encounter the enhancing effect of the preceding sinus beat and thus be precipitated prematurely.

4. It is suggested that the form of extrasystolic bigeminal rhythm described may constitute a link between parasystolic and extrasystolic rhythm.

## Acknowledgment

We gratefully acknowledge the able technical assistance of Miss Rosemary Siford, Miss Bernice Haber and Mrs. Glenda Thompson.

## Addendum

The phenomenon of *concealed bigeminy*, as has been described, is apparently not uncommon if its manifestations are known and looked for. Since completing this article, we have encountered five additional examples: one in a further patient with intermittent parasystole alternating with extrasystolic rhythms (similar to Cases 1 and 2), and four in patients with solely extrasystolic arrhythmias (similar to Case 3).

## References

1. Scherf, D. and Boyd, L. J. Three unusual cases of parasystole. *Am. Heart J.*, 39: 650, 1950.
2. Mueller, P. and Baron, B. Clinical studies on parasystole. *Am. Heart J.*, 45: 441, 1953.
3. Langendorf, R. and Pick, A. Mechanisms of intermittent ventricular bigeminy. II. Parasystole, and parasystole or re-entry with conduction disturbance. *Circulation*, 11: 431, 1955.
4. Katz, L. N. and Pick, A. Clinical Electrocardiography. Part I. The Arrhythmias, p. 147. Philadelphia, 1956. Lea & Febiger.
5. Scherf, D., Schott, A., Reid, E. C. and Chamsai, D. G. Intermittent parasystole. *Cardiologia*, 30: 217, 1957.
6. Schamroth, L. Electrocardiographic effects of eyeball compression. *Am. J. Cardiol.*, 2: 321, 1958.
7. Scherf, D. and Schott, A. Parasystole durch einfache Interferenz mit Übergang in Bigeminie. *Klin. Wchnschr.*, 9: 2191, 1930.
8. Vedoya, R. and Battini, A. Un caso de pararritmia mostrando el mecanismo que conduce al bigeminismo extrasistolico. *Rev. argent. cardiol.*, 6: 313, 1939.
9. Kaufman, R. and Rothberger, C. J. Beiträge zur Kenntnis der Entstehungsweise extrasystolischer Allorhythmien. *Ztschr. ges. exper. Med.*, 7: 199, 1919.
10. Kaufman, R. and Rothberger, C. J. Beiträge zur Kenntnis der Entstehungsweise extrasystolischer Allorhythmien. *Ztschr. ges. exper. Med.*, 11: 40, 1920.
11. Scherf, D. Zur Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien. *Ztschr. ges. exper. Med.*, 51: 816, 1926.
12. Scherf, D. Weitere Untersuchungen über die Entstehungsweise der Extrasystolen. *Ztschr. ges. exper. Med.*, 58: 221, 1927.
13. Piccione, F. V. and Scherf, D. Rhythmic formation of coupled beats and paroxysmal tachycardias in outer layers of myocardium. *Bull. N. Y. Med. Coll.*, 3: 83, 1940.
14. Zander, E. Ein Fall von extrasystolischer Bigeminie mit eigenartiger Kupplungszeit. *Acta med. scandinav.* 66: 189, 1927.
15. Scherf, D. and Schott, A. Extrasystoles and Allied Arrhythmias. Fig. 130. London, 1953. William Heinemann.
16. Mack, I. and Langendorf, R. Factors influencing the time of appearance of premature systoles (including a demonstration of cases with ventricular premature systoles due to re-entry but exhibiting variable coupling). *Circulation*, 1: 910, 1950.
17. Vedoya, R. Parasistolia. Análisos de los complejos mixtos en un caso que presenta bloqueo de rama derecha y actividad de un paracentro situada en el ventriculo derecho. *Rev. argent. cardiol.*, 13: 224, 1946.
18. Scherf, D. and Schott, A. Reference 15, p. 173.
19. Draper, M. H. and Weidmann, S. Cardiac resting and action potentials recorded with an intracellular electrode. *J. Physiol.*, 115: 74, 1951.
20. Trautwein, W. Temperature effects on Purkinje fiber action potentials measured with an intracellular electrode. Proc. XIX Int. Physiol. Congress, p. 835. Montreal, 1953.
21. Caraboeuf, E. and Boistel, J. L'action des taux éléves de gaz carbonique sur le tissu cardiaque, étudiée à l'aide de microelectrodes intracellulaires. *C.R. Soc. Biol., Paris*, 147: 654, 1953.
22. Brooks, C. M., Hoffman, B. F., Suckling, E. E. and Orias, O. Excitability of the Heart, Chap. v. New York, 1955. Grune & Stratton.
23. Scherf, D. and Schott, A. Reference 15, p. 482.

24. SCHERF, D. The mechanism and treatment of extrasystoles. *Progr. Cardiovasc. Dis.*, 2: 370, 1960.
25. WEDENSKY, N. E. Über die Beziehung zwischen Reizung und Erregung im Tetanus. *Berl. Akad. Wissensch.*, 54: 96, Appendix no. 3., St. Petersburg, 1886.
26. ARVANITAKI, A. Propriétés Rythmiques de la Matiére Vivante. Actualités Scientifiques et Industrielles, p. 761. Paris, 1938. Hermann.
27. WEDENSKY, N. E. Die Erregung, Hemmung und Narkose. *Pflügers Arch. ges Physiol.*, 100: 1, 1903.
28. KAUFMAN, R. and ROTHBERGER, C. J. Beiträge zur Kenntnis der Entstehungsweise extrasystolischer Allorhythmien. *Ztschr. ges. exper. Med.*, 29: 1, 1922.
29. MOBITZ, W. Ueber die verschiedene Entstehungsweise extrasystolischer Arhythmien beim Menschen ein Beitrag zur Frage der Interferenz mehrerer Rhythmen. *Ztschr. ges. exper. Med.*, 34: 490, 1923.
30. SCHERF, D. Zur Frage der Parasystolie. *Wien. Arch. inn. Med.*, 8: 155, 1924.

# Experimental Studies

## Electrocardiographic Patterns Following Interruption of Main and Peripheral Branches of the Canine Right Bundle of His*

HERMAN N. UHLEY, M.D. *and* LAURENCE RIVKIN, M.D.

San Francisco, California

THE MANY STUDIES of transmission of impulses in the mammalian ventricle[1–28] have failed to fully clarify the precise electrocardiographic patterns of localized intraventricular conduction defects. The advent of newer technics has now made it possible to produce localized lesions in the endocardium of the living dog under direct vision and, subsequently, to validate the precise relationship of the lesions to the conduction system. It is the purpose of this study to record and analyze the electrical alterations produced by localized interruption of the main and peripheral branches of the right ventricular conduction system in the dog.

### METHODS

Thirty-seven adult mongrel dogs were used, each being anesthetized with intravenous sodium pentobarbital and placed on a positive pressure respirator. A right thoracotomy was performed and the dogs were placed on total cardiopulmonary bypass utilizing a modified DeWall-Lillehei heart-lung machine. The apparatus was primed with homologous dog blood and perfusion was maintained at 100 ml. per kg. per minute. The body temperature was maintained at 37° c. Electrocardiograms (ECG) and vectorcardiograms (VCG) were obtained using a modified cube system of electrical recording. The superior-inferior (S-I) recording axis was formed by electrodes in the right posterior axillary line at the level of the shoulder (−) and at the lower margin of the rib cage (+). A posterior-anterior (P-A) recording axis was formed by the lower electrode of the S-I axis (−) and a second electrode at the same level in the right anterior axillary line (+). The right-left (R-L) recording axis also utilized the lower electrode of the S-I axis (−) in combination with an electrode at the same level in the left posterior axillary line (+). Scalar recordings were made by amplifying the voltages from a given axis with a Tektronix-122 preamplifier and by recording the output on a Hewlitt-Packard 130A oscilloscope. The 20 msec. per cm. sweep was used for temporal measurements. Vector recordings were made by amplifying the voltage from two of the three axes with two Tektronix-122 preamplifiers which, in turn, fed into the respective horizontal and vertical amplifiers of the Hewlitt-Packard 130A oscilloscope. A switch arrangement from the various axes permitted recording of the frontal, sagittal and horizontal planes. Permanent recordings were made with a DuMont-302 Polaroid camera.

A ventriculotomy incision 2 to 3 cm. long was made in either the anterior, middle or posterior portion of the right ventricular wall, avoiding the larger coronary arteries. One or more superficial incisions were then made in the endocardium in the main right bundle, the anterior primary branch, the lateral primary branch, the posterior primary branch; or the upper two-thirds of the septal wall anterior and posterior to the main bundle. These incisions were approximately 5 mm. long.

The electrical recordings were made before and after the incision into the conduction system or septal wall. Following the termination of the procedure the dog was sacrificed and the heart removed. The right ventricular cavity was exposed and washed. Lugol's iodine solution was applied to the endocardial surface, thereby staining the conduction system and verifying its exact relationship to the incision.

* From the Departments of Surgery and Pathology, Harold Brunn Institute, Mount Zion Hospital and Medical Center, San Francisco, California. Aided by grants from the National Heart Institute, and National Institutes of Health (H-3116 and H-4461).

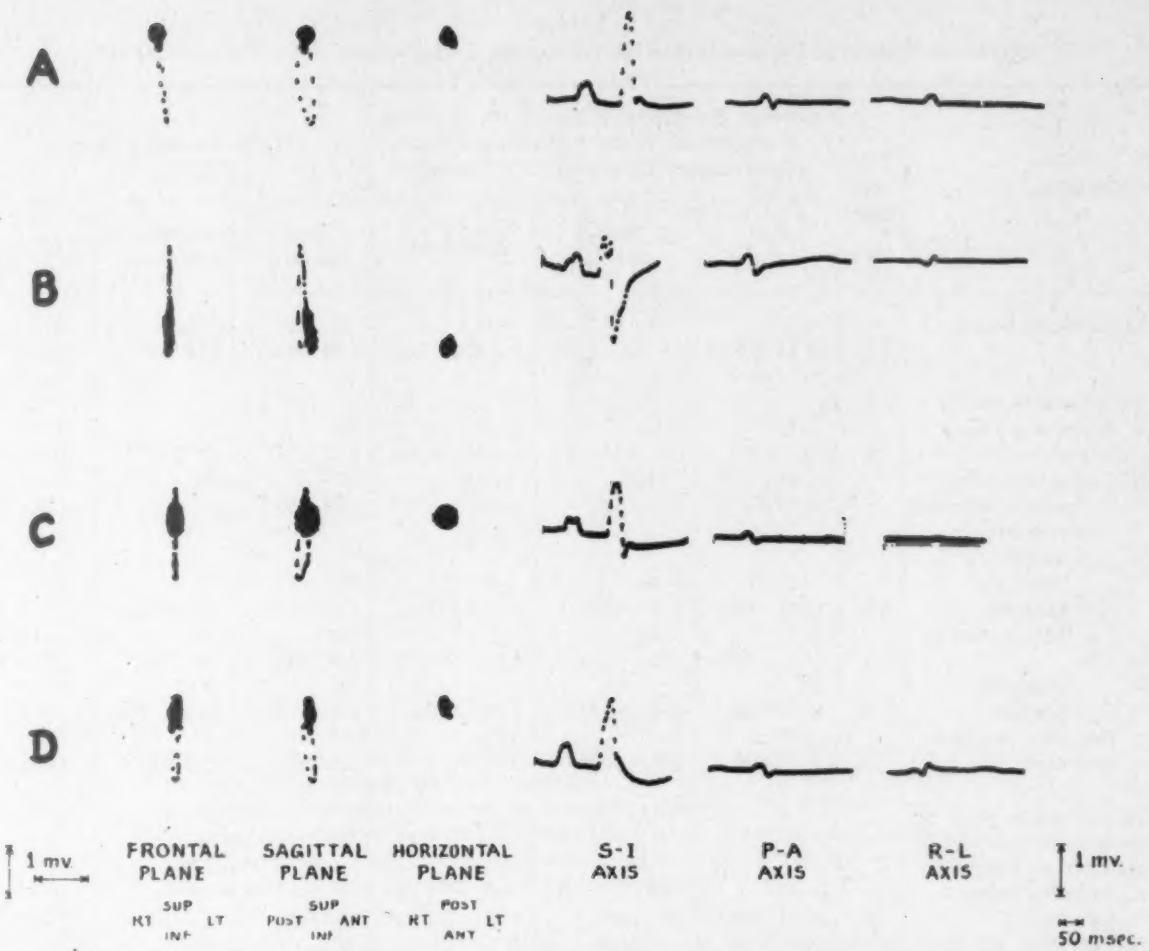



FIG. 1. Representative vectorcardiogram and electrocardiogram patterns. A, controls. B, following incision of the main right bundle of His. C, following incision of the anterior or lateral primary branches. D, following incision of the posterior primary branches. The VCG trace is interrupted each 2.5 msec. and the narrow edge of the tear drop indicates the direction of inscription.

Photographs were taken before the staining disappeared. The lesions were grouped anatomically, and then correlated with the electrical alterations.

## RESULTS

### CONTROL PATTERNS

The normal VCG pattern (Fig. 1A) generally was characterized by small initial and large body forces directed inferiorly, slightly anteriorly and to the left, and terminal forces directed either superiorly or inferiorly, and slightly posteriorly and to the right. The normal ECG pattern (Fig. 1A) in the S-I axis was characterized by a tall R wave followed by a much smaller wave at the base of the downstroke of the R wave (r′) or a small s wave, and small rs waves in the P-A and R-L axes. The average QRS duration was 50 msec.

### PATTERNS FOLLOWING INCISION OF THE MAIN BRANCH OF THE RIGHT BUNDLE OF HIS

Of the three scalar leads recorded (Fig. 1B), the S-I axis exhibited the most striking changes in contour following incision of the conduction system. These changes principally involved the last portion of the QRS complex, corresponding to the terminal forces of the VCG, and appeared as an alteration of the S wave or the downstroke of the R wave.

Following incision of the right main bundle of His, the body and particularly the terminal forces of the VCG were markedly accentuated superiorly (Fig. 1B). There was slight accentuation of the terminal forces posteriorly and to the right and, occasionally, to the left. In addition, the inscription of the terminal forces was considerably delayed.

In the ECG the average relative amplitude of

TABLE I

Alterations Following Incision of Specific Sites in the Endocardium of the Right Ventricle

| Site of Incision | No. of Dogs | Average Relative r′ Wave (+) or S Wave (−) Amplitude in the S-I Axis (expressed as percentage of the total R + S waves) | | | QRS Duration (msec.) | | |
|---|---|---|---|---|---|---|---|
| | | Pre-incision | Post-incision | Difference | Pre-incision | Post-incision | Difference |
| 1. Main right bundle | 16 | −13 (13/−45)* | −59 (−33/−89) | −46† (−27/−84) | 49 (38/58) | 70 (56/80) | 21† (8/42)† |
| 2. Peripheral branches | | | | | | | |
| a. Anterior primary branches | 4 | −10 (5/−21) | −48 (−44/−51) | −38‡ (−29/−56) | 60 (57/62) | 61 (57/64) | 1 (0/3) |
| b. Lateral branches | | −11 | −42 | −31§ | 57 | 56 | −1 |
| Primary branches | 6 | (17/−71) | (0/−82) | (−11/−73) | (47/66) | (47/63) | (3/−6) |
| Secondary branches | | | | | | | |
| Anterior portion | 18 | −6 (14/−45) | −8 (13/−44) | −2 (7/−23) | 55 (36/60) | 55 (36/62) | 0 (2/−2) |
| Midportion | 9 | −9 (14/−50) | −24 (17/−71) | −15‡ (3/−40) | 50 (44/58) | 49 (47/58) | −1 (0/−4) |
| Posterior portion | 4 | 0 (13/−9) | 2 (11/−15) | 2 (19/−10) | 50 (42/−58) | 50 (42/−88) | 0 (0/0) |
| c. Posterior primary branches | 5 | −10 (0/−18) | 9 (21/−7) | 19‡ (29/8) | 47 (32/56) | 47 (32/56) | 0 (0/0) |
| 3. In the septal wall in areas grossly devoid of conduction fibers | | | | | | | |
| a. Anterior septal incision | 7 | −11 (11/−38) | −13 (5/−45) | −3 (1/−7) | 56 (36/64) | 56 (38/62) | 0 (2/−2) |
| b. Posterior septal incision | 5 | −7 (11/−28) | −7 (4/−25) | 0 (3/−7) | 48 (40/52) | 48 (40/50) | 0 (0/2) |

* Figures in parentheses indicate range.
† $p < 0.001$.
‡ $p < 0.01$.
§ $p < 0.05$.

the S waves in the S-I axis increased from 13 per cent to 59 per cent of the total R + S wave amplitude and the duration of the QRS complex increased an average of 21 msec. (Table I). In the P-A and R-L axes the most conspicuous changes from the control tracings were the prolongation of the QRS duration and a slight accentuation of the terminal portion of the QRS complex.

### PATTERNS FOLLOWING INCISIONS OF THE PERIPHERAL BRANCHES OF THE RIGHT BUNDLE OF HIS

#### 1. *The Anterior Primary Branches*

In the VCG (Fig. 1C), the terminal forces developed a superiorly-oriented appendage without any significant delay following incision of the anterior primary branch of the right bundle of His; in the ECG the relative amplitude of the S wave in the S-I axis increased from an average of 10 per cent to an average of 48 per cent of the total R + S wave amplitude (Table I). Significant changes in the other axes were not apparent; there was no significant prolongation of the QRS complex.

#### 2. *The Lateral Branches*

*a. Lateral primary branches (Fig. 1C):* Following incision of the lateral primary branches of the right bundle of His the terminal forces in the VCG developed a superiorly-oriented appendage but there was no significant terminal delay. In the ECG the average relative amplitude of the S wave in the S-I axis increased from 11 per cent to 42 per cent of the total

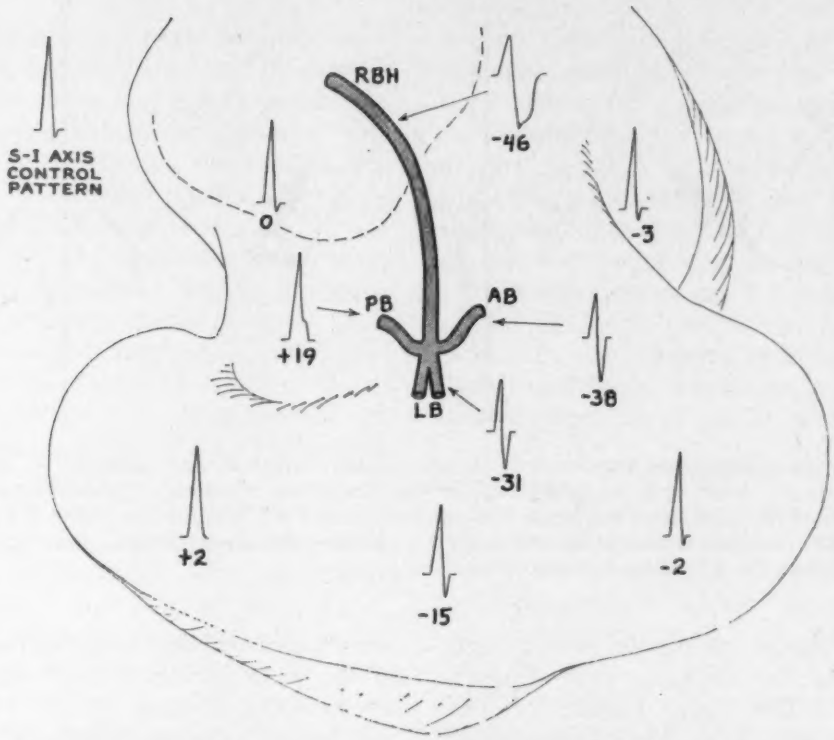



FIG. 2. Summary of the contour changes observed in the S-I axis following incision at various sites in the endocardium of the right ventricle. The number indicates the difference between the average relative r′ (+) or s (−) wave amplitude (expressed as percentage of the total R + S waves) prior to and following incision. (RBH = right bundle of His. AB, LB and PB = anterior, lateral and posterior primary branches, respectively.)

R + S wave amplitude (Table 1). There was no significant increase of QRS duration or apparent change in the other axes.

*b. Lateral secondary branches:* Anterior portion of the right ventricular wall.* There were no significant changes from the control patterns in either the VCG or ECG (Table 1).

*Midportion of the right ventricular wall.* Following ventriculotomy incisions into the midportion of the right ventricular wall the terminal forces in the VCG increased superiorly without significant delay and in the ECG, the average relative amplitude of the S waves in the S-I axis increased from 9 per cent to 24 per cent of the total R + S wave amplitude (Table 1).

*Posterior portion of the right ventricular wall.* There were no significant changes from the control patterns either in the VCG or ECG (Table 1).

### 3. *The Posterior Primary Branches*

After incision of the posterior primary branches of the right bundle of His, the terminal forces in the VCG developed an inferior orientation and tended to be oriented more toward the right (Fig. 1D). There was no significant delay in the inscription of the terminal forces. In the ECG the average relative amplitude of the S wave in the S-I axis prior to incision of the posterior primary branch of the right bundle of His was 10 per cent of the R + S amplitude. Following the incision the S wave was replaced by an r′ wave, 9 per cent of the total R + S wave amplitude (Table 1), and in the R-L axis there was a tendency for the s wave to be more prominent or the late r wave to be smaller than its control. No significant increase in QRS duration was observed.

* Branches lying in the subendocardium of the right ventricular wall divided by the ventriculotomy incision.

#### PATTERNS FOLLOWING INCISION IN THE SEPTAL WALL IN AREAS GROSSLY DEVOID OF THE CONDUCTION SYSTEM

There were no significant changes in the VCG or ECG (Table 1) following incision into the upper two-thirds of the septal wall.

## COMMENTS

In a previous study[29] the main and peripheral

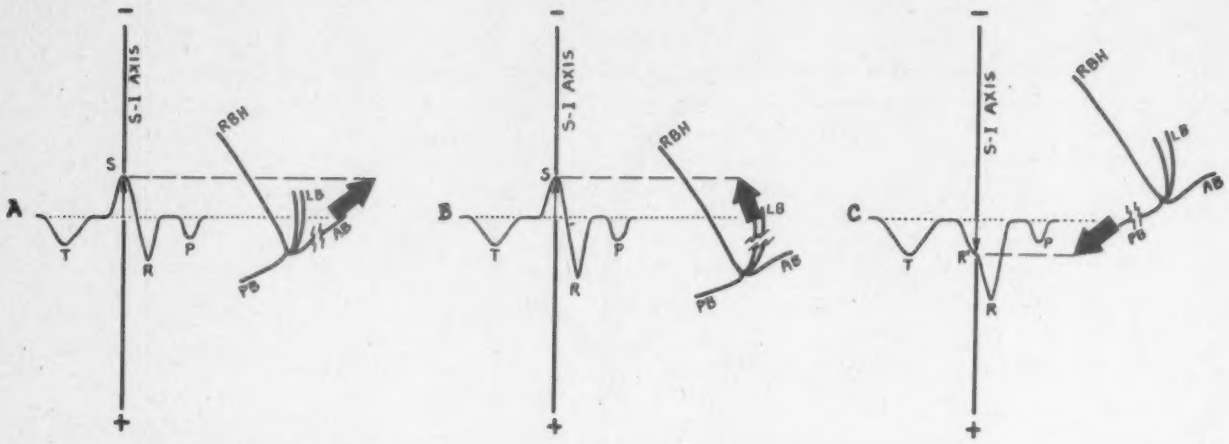



FIG. 3. A possible explanation for the characteristic electrical changes observed on cutting the (A) anterior, (B) lateral and (C) posterior primary branches of the right bundle of His. Incision of a branch of the conduction system deprives a given area of its usual rapid means of activation and results in spread of the activation process relatively slowly from adjacent muscle. The resultant vectors so formed appear as characteristically oriented terminal forces (thick arrows) which when projected on the S-I axis gives rise to S waves or r′ waves.

branches of the canine conduction system were grossly visualized by staining with Lugol's iodine solution. The right bundle of His appeared on the right septum as a long narrow band arising under the medial leaflet of the tricuspid valve. It then extended to the anterior papillary muscle where it formed anterior primary branches, several large lateral primary branches and posterior primary branches. These branches, particularly the lateral branches, were observed to ramify extensively over the free wall of the right ventricle. There was an absence of grossly visible conduction fibers on the upper two-thirds of the septum except for the narrow right main bundle.

In the present study it has been noted that interruption of the main or larger peripheral branches of the conduction system in the right ventricle of the dog resulted in consistent and characteristic alterations in the electrical patterns (Fig. 2). The principal changes occurred in the terminal portion of the QRS complex or the corresponding terminal forces of the vectorcardiogram. As expected, when the right main bundle was cut, marked prolongation of the QRS complex was observed. By contrast, no significant increase in QRS duration was observed when the peripheral branches were cut. In addition there was marked alteration in the QRS contour following division of the main right bundle, characterized by a large increase in the amplitude of the S wave. Concomitantly, the terminal forces were markedly accentuated superiorly.

When either the anterior or the lateral primary branches were cut there was an increase in the terminal forces superiorly, resulting in an increased S wave in the S-I axis. When the posterior primary branches were cut the terminal forces were directed inferiorly and the S wave in the S-I axis became an r′ wave.

Incisions in the anterior and posterior portion of the free right ventricular wall did not result in any significant change in the VCG or ECG. Incisions in the midportion of the right ventricular wall resulted in terminal force and S wave changes similar to but of smaller degree than those seen on cutting the primary lateral branches, apparently due to a concentration of secondary ramifications of the lateral peripheral branches in this region.

When incisions were made in the upper two-thirds of the right ventricular septum no significant changes were seen and no conduction fibers could be visualized grossly in this area in the stained specimens.

*Mechanism for Changes in Electrical Patterns:* A reasonable explanation for the observed electrical changes has been considered: When the anterior primary, lateral primary or posterior primary branches are cut, the portions of the heart normally activated by that segment of the conduction system were deprived of their usual means of rapid activation (Fig. 3). Instead, the involved areas were activated at a lower rate by the propagation of the activation wave from adjacent cardiac muscle fibers. When the anterior and lateral primary branches were divided, the activation wave spread through these areas in a superior direction.

Consequently, the resultant of the terminal force vectors would be expected to project on the S-I axis in a negative direction, giving rise to the observed S waves. When the posterior primary branch was interrupted the area it formerly supplied was activated by contiguity from the adjacent muscle, resulting in inferiorly-directed vectors appearing after most of the heart was activated. Hence, the projection of the resultant of these terminal force vectors on the S-I axis resulted in positively-directed forces or the formation of an r′ wave. This explanation of the changes in contour are analogous to the patterns of "peri-infarction block" in the left ventricle.[30–35]

*Change in QRS Duration:* The duration of the QRS complex was not significantly increased when the peripheral branches were cut. This suggests that areas deprived of their usual rapid means of activation were still able to be depolarized before the last portion of the normally activated heart was depolarized. The last portion of the canine septum to be activated is the superior-posterior portion of the right septum[36] and the closest peripheral conduction fibers that can be seen by gross staining technics[29] are the posterior branches of the left bundle or the posterior and lateral branches of the right bundle. If the velocity of conduction in muscle is approximately 400 mm. per second and about 2 cm. exists between the closest peripheral fibers and the last portion of the septum to be activated, 50 msec. should be required for the depolarization process to be completed. Accordingly, the normal QRS duration observed in this study averaged 50 msec. It can be implied that peripheral conduction defects result in delays which do not necessarily exceed the time normally taken by the depolarization process, traveling relatively slowly through the muscle of the upper septum to completely depolarize the heart.

*Clinical Application:* If the present results were to be given clinical application, they suggest that localized defects in the peripheral conduction system can be suspected when certain changes are seen in the contour of the last portion of the QRS complex, even in the absence of prolongation of the QRS duration. Assuming fundamental similarity in the canine and human conduction systems, defects in the anterior and lateral branches of the right ventricular conduction system might result in the appearance of terminal force changes directed anteriorly and rightward, whereas posterior branch defects might result in terminal force changes directed posteriorly. Consequently, in a right-sided precordial lead such as $V_1$, one would expect a complex characterized by an rSr′ to result from defective conduction in the anterior or lateral primary branches of the right bundle, the r′ being due to the component of the late forces approaching the electrode. On the other hand, an rS complex with a slurring of the S wave would result from conduction defects in the posterior branch, the slurred S wave being due to late forces moving posteriorly or away from the precordial electrode.

## Summary

The main and peripheral branches of the right ventricular conduction system of the dog were interrupted under direct vision using the cardiopulmonary bypass technic. This resulted in characteristic alterations of the recorded electrical forces. The principal result of cutting the main branch of the right bundle was prolongation of the QRS complex with a marked accentuation of the terminal QRS forces superiorly. The major electrocardiographic change was the occurrence of a prominent S wave in the S-I axis. In contrast, cutting the peripheral branches of the right bundle of His did not result in any significant QRS prolongation. However, when the anterior or lateral branches were cut the terminal forces increased superiorly and corresponding increased S waves occurred in the S-I axis. Conversely, when the posterior branches were cut the terminal forces were directed inferiorly and a slurring (r′) appeared on the downstroke of the R wave in the S-I axis. Incisions in the upper two-thirds of the right septum, which is devoid of grossly visible peripheral conduction fibers, did not result in any significant change. A possible mechanism for the observed electrical patterns is discussed. It is suggested that it may be possible to localize small right septal lesions in man by the appearance of the terminal QRS forces.

## References

1. Eppinger, H. and Rothberger, J. Ueber die Folgen der Durchschneidung der Tawarschen Schenkel des Reizleitung Systems. *Ztschr. klin. Med.*, 70: 1, 1910.
2. Rothberger, C. J. and Winterberg, H. Zur Diagnose der einseitigen Blockierung in den Tawaraschen Schenkeln. *Zentralbl. f. Herz u. Gefasskr.*, 5: 206, 1913.
3. Lewis, T. and Rothschild, M. A. The excitatory process in the dog's heart. II. The ventricle.

*Phil. Tr. Roy. Soc. London*, 206: 181, 1915.

4. Lewis, T. The spread of the excitatory process in the vertebrate heart. *Phil. Tr. Roy. Soc. London*, 207: 221, 1916.
5. Oppenheimer, B. S. and Rothschild, M. A. Electrocardiographic changes associated with myocardial involvement. *J.A.M.A.*, 69: 429, 1917.
6. Wilson, F. N. and Herrmann, G. R. Bundle branch and arborization block. *Arch. Int. Med.*, 26: 153, 1920.
7. Smith, F. M. Experimental observations on the atypical QRS waves of the electrocardiogram of the dog. *Arch. Int. Med.*, 26: 205, 1920.
8. Wilson, F. N. and Herrmann, G. R. An experimental study of incomplete bundle branch block and the refractory period of the heart of the dog. *Heart*, 8: 229, 1921.
9. Wilson, F. N., Macleod, A. G. and Barker, P. S. The order of ventricular excitation in human bundle branch block. *Am. Heart J.*, 7: 305, 1932.
10. Abramson, D. I. and Jochin, K. The spread of the impulse in the mammalian ventricle. *Am. J. Physiol.*, 120: 635, 1937.
11. Weinberg, H. B. and Katz, L. N. Two unusual types of electrocardiograms. *Am. Heart J.*, 19: 519, 1940.
12. Harris, A. S. The spread of the excitation in turtle, dog, cat and monkey ventricles. *Am. J. Physiol.*, 134: 319, 1941.
13. Segers, M. The different types of intraventricular block. *Am. Heart J.*, 37: 92, 1949.
14. Rosenman, R. H., Pick, A. and Katz, L. N. The electrocardiographic patterns and the localization of intraventricular conduction defects. *Am. Heart J.*, 40: 845, 1950.
15. First, S. R., Bayley, R. N. and Bedford, D. R. Peri-infarction block. *Circulation*, 2: 31, 1950.
16. Sodi-Pallares, D., Rodriques, M. I., Chait, L. O. and Zuckerman, R. The activation of the intraventricular septum. *Am. Heart J.*, 41: 569, 1951.
17. Pruitt, R. D., Essex, H. E. and Burchell, H. B. Studies on the spread of excitation through the ventricular myocardium. *Circulation*, 3: 418, 1951.
18. Burchell, H. B., Essex, H. E. and Pruitt, R. D. Studies on the spread of excitation through the ventricular myocardium. II. The ventricular septum. *Circulation*, 6: 161, 1952.
19. Rodriques, M. I. and Sodi-Pallares, D. The mechanism of complete and incomplete bundle branch block. *Am. Heart J.*, 44: 715, 1952.
20. Scher, A. M., Young, A. C., Malmgreen, A. L. and Paton, R. R. Spread of electrical activity through the wall of the ventricle. *Circulation Res.*, 1: 539, 1953.
21. Alzamoro-Castro, V., Abugattas, R., Rubio, C., Bouroncle, J., Zapata, C., Santa-Maria, E., Battilana, G., Binder, T., Subiriá, R. and Paredes, D. Parietal focal block. An experimental and electrocardiographic study. *Circulation*, 7: 108, 1953.
22. Kennamer, S. R. and Prinzmetal, M. Depolarization of the ventricle with bundle branch block; studies on the mechanism of ventricular activity. X. *Am. Heart J.*, 47: 769, 1954.
23. Smith, L. A., Kennamer, S. R. and Prinzmetal, M. Ventricular excitation in segmental and diffuse types of experimental bundle branch block. *Circulation Res.*, 2: 221, 1954.
24. Scher, A. M., Young, A. C., Malmgreen, A. L. and Erickson, R. B. Activation of the interventricular septum. *Circulation Res.*, 3: 56, 1955.
25. Sodi-Pallares, D., Bisteni, A., Medrano, G. A. and Cisneros, F. The activation of the free left ventricular wall in the dog's heart: in normal conditions and in left bundle branch block. *Am. Heart J.*, 49: 587, 1955.
26. Medrano, G. A., Bisteni, A., Brancato, R. W., Pileggi, F. and Sodi-Pallares, D. The activation of the interventricular septum in the dog's heart under normal conditions and in bundle branch block. *Ann. New York Acad. Sci.*, 65: 804, 1957.
27. Scher, A. M. and Young, A. C. Ventricular depolarization and the genesis of QRS. *Ann. New York Acad. Sci.*, 65: 768, 1957.
28. Durrer, D. and Van der Tweed, L. H. Excitation of the left ventricular wall of the dog and goat. *Ann. New York Acad. Sci.*, 65: 779, 1957.
29. Uhley, H. N. and Rivkin, L. M. Peripheral distribution of the canine A-V conduction system. *Am. J. Cardiol.*, 5: 688, 1960.
30. Grant, R. P. and Murray, R. H. QRS deformity in myocardial infarction in the human subject. *Am. J. Med.*, 17: 587, 1954.
31. Grant, R. P. and Dodge, H. T. Mechanism of QRS complex prolongation in man; left ventricular conduction defects. *Am. J. Med.*, 20: 8311, 1956.
32. Dodge, H. T. and Grant, R. P. Right ventricular conduction defects. *Am. J. Med.*, 21: 534, 1956.
33. Grant, R. P. Left axis deviation: an electrocardiographic-pathologic correlation study. *Circulation*, 14: 233, 1956.
34. Grant, R. P. Left axis deviation. *Mod. Concepts Cardiovas. Dis.*, 17: 437, 1958.
35. Grant, R. P. Peri-infarction block. *Progr. Cardiovas. Dis.*, 2: 237, 1959.
36. Amer, N. S., Stuckey, J. H., Hoffman, R. F., Cappelletti, R. R. and Domingo, R. T. Activation of the interventricular septal myocardium studied during cardiopulmonary bypass. *Am. Heart J.*, 59: 224, 1960.

# The Effect of Hyperpotassemia on the Idioventricular Pacemaker in Complete A-V Heart Block and Comparison with Its Effect on the Heart Rate in Normal Sinus Rhythm

## An Experimental Study in Dogs*

OTTO F. MULLER, M.D., ANTONIO C. DELEON, JR., M.D. *and* SAMUEL BELLET, M.D., F.A.C.C.
Philadelphia, Pennsylvania

THE PURPOSE OF THIS STUDY was to investigate the effect of hyperpotassemia on the ventricular pacemaker in complete A-V heart block. Many studies are available concerning the effect of hyperpotassemia on the cardiac pacemaker in human subjects and animals with normal sinus rhythm,[1-12] but there are relatively few isolated observations relative to the association of hyperpotassemia and complete A-V heart block.[13-15] This association is not uncommon and would appear to have some clinical significance. We have recently had the opportunity of observing four patients with complete A-V heart block who had episodes of Stokes-Adams seizures with the advent of acidosis and/or elevation of the serum potassium level.[16] Although hyperpotassemia may develop in the presence of acidosis, these two alterations do not necessarily occur in the same patient. Moreover, the experimental production of acidosis may or may not be associated with an increase in serum potassium values.[17] Acidosis alone appears to have relatively little effect on the ventricular rate in normal sinus rhythm.[18] On the other hand, acidosis profoundly depresses the ventricular pacemaker in the presence of complete A-V heart block.[17] Because of our clinical observations the following studies were performed to determine the effect of hyperpotassemia on the ventricular pacemaker in complete A-V heart block.

### METHODS AND MATERIAL

Seventeen healthy mongrel dogs with weights between 9.8 and 16.3 kg. were used in these experiments. All animals were anesthetized prior to the experiment with pentobarbital sodium (30 mg. per kg.) administered intravenously and artificial respiration was instituted by means of a positive pressure breathing apparatus delivering compressed air at a respiration rate of 15 to 20 per minute. Both kidney pedicles, including the renal artery and vein, were approached through an upper abdominal midline incision, freed from the supporting structures and ligated with No. 1-0 silk sutures. Thereafter, the abdominal incision was closed with interrupted silk sutures. The purpose of excluding the kidneys from the circulation was to maintain more easily a steady plasma potassium increment; this is difficult to attain in the animal with normally functioning kidneys. Isotonic potassium chloride (1.14 per cent solution) was infused into the femoral vein at a rate of 5 cc. per minute, usually over a period of twenty to sixty minutes. Control records with simultaneous electrocardiograms, intra-arterial blood pressure tracings and arterial serum electrolytes (pH, K, Cl, Na) were obtained and these studies repeated at various intervals during the continuous infusion of potassium chloride. A correlation was made between the various electrocardiographic alterations

* From the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania, and the Robinette Foundation of the University of Pennsylvania. This work was supported by a grant from the U. S. Public Health Service, H141 (C-9) and the Eli Lilly Company, Indianapolis, Indiana.

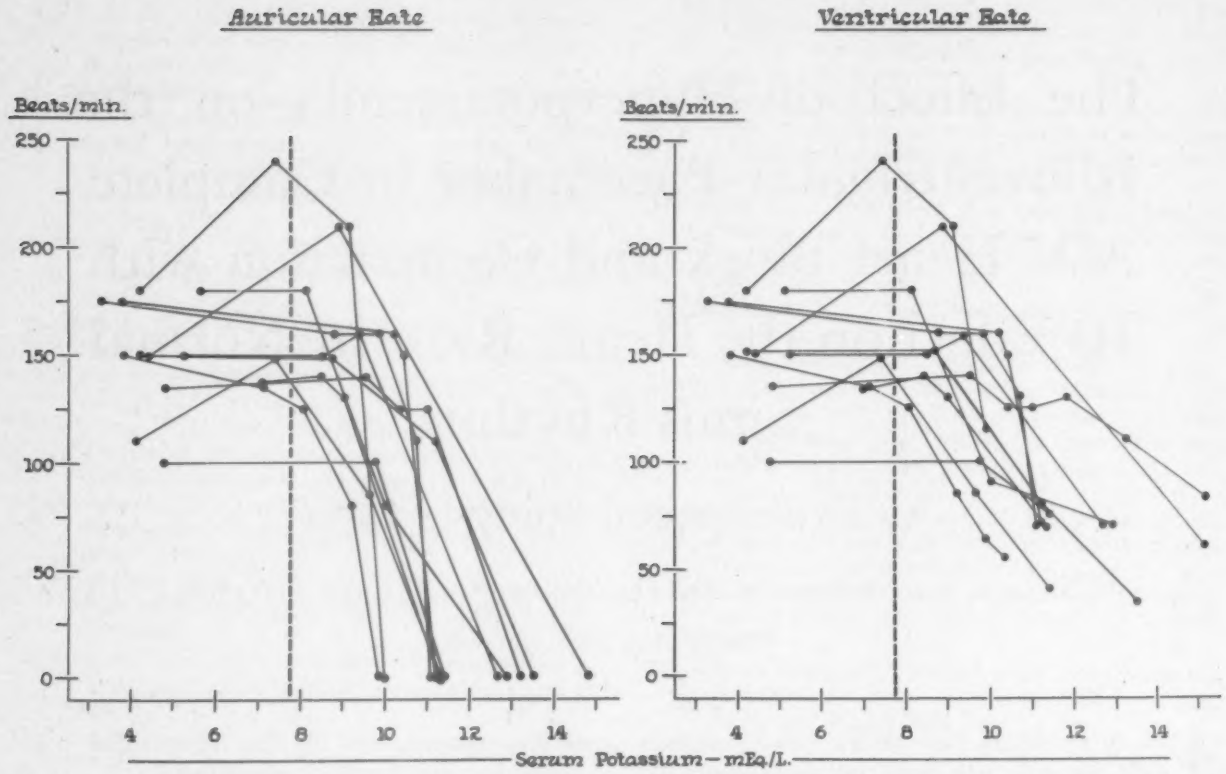



FIG. 1. The effect of hyperpotassemia on the atrial and ventricular rate in dogs with normal sinus rhythm. Note the relatively insignificant change in heart rate up to serum potassium levels of 9.2 mEq./L. Atrial standstill occurs abruptly at a serum potassium level between 9.8 and 14.9 mEq./L. Slowing of the ventricular rate takes place at comparable serum potassium levels (10 to 14 mEq./L.).

and these electrolytes, especially the serum potassium values.

Twelve experiments were performed in nine healthy mongrel dogs with normal sinus rhythm and eleven experiments were performed in eight dogs with complete A-V heart block.

Complete A-V heart block was produced in eight of the seventeen dogs by a method previously employed in this laboratory,[17] namely, the injection of formalin into the A-V node by an approach through the right atrium. A two week period of observation of these animals was allowed during which time it was determined that the A-V block was complete and permanent.

Electrolyte determinations were performed by methods previously described in this laboratory.[18] The variations in value obtained in control samples in our laboratory are ±0.2 mEq./L. for potassium, ±2 to 3 mEq./L. for sodium and ±1 to 2 mEq./L. for chlorides.

## RESULTS

*Effect of Potassium Chloride Infusion on the Heart Rate in the Presence of Normal Sinus Rhythm:* The effect of hyperpotassemia on the atrial and ventricular rates in nine dogs with normal sinus rhythm is shown in Figure 1. It will be observed that there is relatively little effect on the heart rate with serum potassium levels up to 9.2 mEq./L. (±0.7 mEq./L.). In four experiments the rates remained unchanged, there was an average increase of 12.2 per cent in five and in four the average decrease was 14.3 per cent from the control rate. A significant slowing of the ventricular rate occurred in the presence of normal sinus rhythm when the serum potassium levels exceeded 9 to 10 mEq./L. In eight of the twelve experiments, even with high plasma levels ranging between 11.5 and 15 mEq./L., the ventricular rate remained between 70 to 90 per minute. In only two of the twelve experiments did the rate decrease below 50 per minute, at serum potassium levels of 11.5 and 13.8 mEq./L. The atrial rate paralleled the ventricular rate fairly closely in the early stages of hyperpotassemia. Thereafter, there was a tendency for slowing of the atrial rate, with the final abolition of the atrial complexes during the latter part of stage 3 and particularly in stage 4 hyperpotassemia,[1] at serum levels of 9.8 to 14.9 mEq./L. (Fig. 2).

Following the infusion of potassium chloride, in addition to the serum potassium increment the following electrolyte alterations were ob-

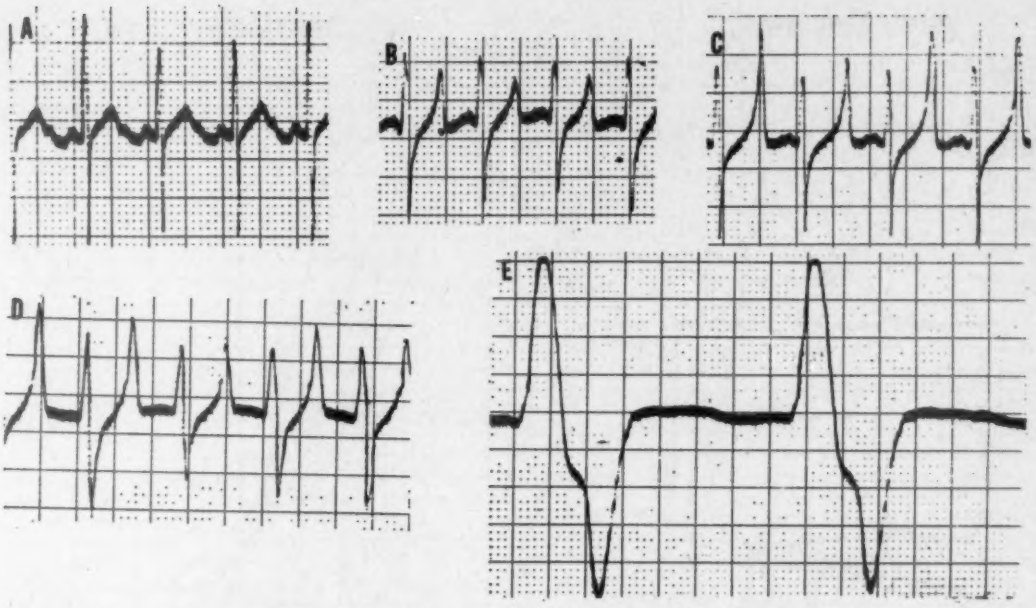



FIG. 2. The effect of potassium infusion in a typical experiment on the atrial and ventricular rate in the presence of normal sinus rhythm. A, control, lead II; rate, 150 per minute; serum potassium, 3.75 mEq./L. B, following potassium infusion, the serum potassium level has increased to 10.42 mEq./L. Rate is 150 per minute. Note the lowering in amplitude of P, slight widening of QRS and increase in amplitude of T. C, serum potassium is increased to 11.80 mEq./L. Ventricular rate is 130 per minute. Note the conspicuous widening of the QRS (0.12 second) and flat, broad P waves and typical tall peaked T waves. D, the serum potassium is 13.24 mEq./L. Note the marked widening of the QRS complexes and the absence of atrial activity. The ventricular rate is 110 per minute. E, the serum potassium is 17.50 mEq./L. Note the slow idioventricular rhythm (40 per minute). Death occurred in cardiac arrest.

served: (1) the pH was relatively unchanged; (2) the sodium level in some of the animals was increased as high as 8 mEq./L. but was decreased to almost a similar degree in other experiments; in about half of these animals the sodium level was unchanged; (3) the chlorides were increased in a range of 2 to 6 mEq./L.; and (4) no significant alterations were observed in serum calcium levels.

*Effect of Potassium Chloride on the Atrial Rate in Complete A-V Heart Block:* The effect of hyperpotassemia on the atrial rate in dogs with complete A-V heart block is shown in Figure 3. During the initial stages of hyperpotassemia with the serum potassium level up to 7.75 mEq./L. (±0.22 mEq./L.) the changes in the atrial rate were insignificant, usually increasing slightly. There was no change in four experiments; an average increase of 13.3 beats per minute (9.1 per cent of the control rate) in six; and a decrease of 10 beats per minute (7 per cent of the control rate) in one experiment. At higher serum potassium levels (8.31 to 11.3 mEq./L.) there was a rapid decrease of the atrial rate and atrial standstill occurred quickly. In most instances atrial standstill was observed with serum potassium levels between 9.3 and 11.5 mEq./L. (Fig. 3).

*Effect of Potassium Chloride on the Ventricular Rate in Complete A-V Heart Block:* The control ventricular rate in nine dogs with complete A-V heart block averaged 48 per minute (range, 28 to 70 per minute). Following infusion of potassium chloride the rate of the ventricular pacemaker decreased by 24.5 beats per minute or 51 per cent (±3.61 per cent) of the control rate. This slowing occurred during the initial stages of hyperpotassemia, with increase of serum levels up to 7.75 mEq./L. (±0.22 mEq./L.). In seven of the eleven experiments the most precipitous drop in rate was observed with serum potassium levels below 6.5 mEq./L. In only one case was the decrease in ventricular rate less marked (22.2 per cent of the control rate) at a potassium level of 7.5 mEq./L. At higher serum potassium levels the slowing of the ventricular rate was more gradual. At levels between 8.3 and 13.8 mEq./L., the rate decreased on an average of 6.3 beats per minute or 11.4 per cent of the control rate (Fig. 3). T wave changes consisted of marked increase in amplitude, as seen in stage 1 and 2 hyper-

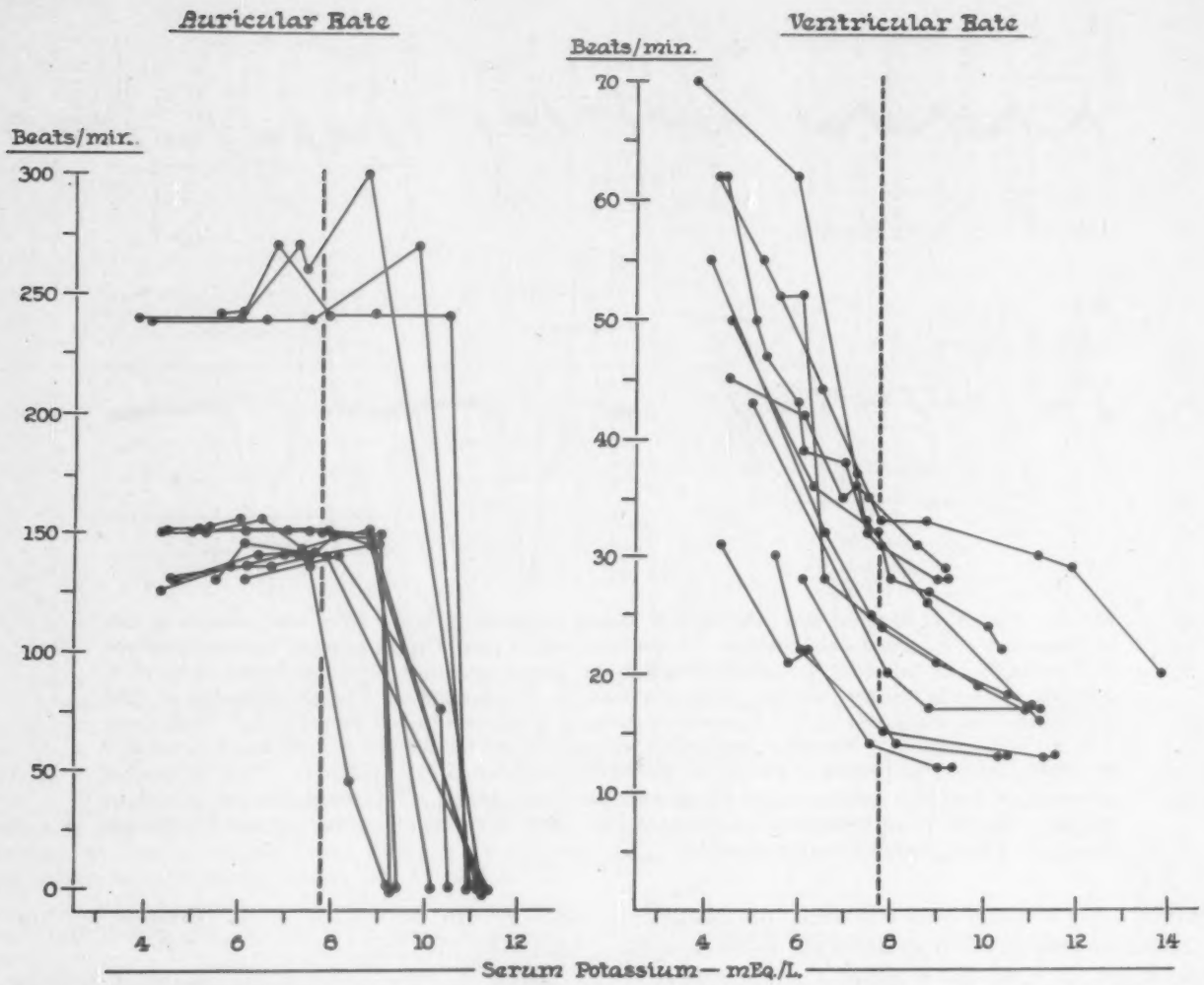



FIG. 3. The effect of hyperpotassemia on the atrial and ventricular rate in dogs with complete A-V heart block. Left, atrial rate response. Note the insignificant changes of rate at a serum potassium level lower than 7.75 mEq./L. Atrial standstill occurred abruptly at serum potassium levels between 9.3 and 11.5 mEq./L. (In eight experiments the control atrial rate ranged from 125 to 150 per minute; in three, however, the atria showed a high control rate of 240, represented by the upper group.) Right, ventricular rate response. Note the marked decrease in rate with moderate potassium increment (lower than 7.75 mEq./L.). At higher potassium levels the decrease is more gradual. The arterial blood pH was maintained within a narrow range (±0.03) during these experiments.

potassemia. These changes were associated with S-T segment depressions particularly in those instances when the increase of T amplitude was marked. Changes in QRS morphology were not observed during the initial stages but marked widening of QRS appeared as a terminal event in association with high serum potassium levels (usually in excess of 11 mEq./L.) (Fig. 4).

The pH was maintained at a relatively constant level within a small range (±0.03) in all eleven experiments so that acidosis, *per se*, could be excluded as a causative factor for the marked slowing of the ventricular rate. The alterations in serum sodium, chloride and calcium levels were similar to those mentioned under the experiments in normal sinus rhythm: (1) serum sodium levels were unaltered in six of the eleven experiments; in four it decreased between 6 and 13 mEq./L.; and in one it increased 9 mEq./L.; (2) serum chloride levels increased between 2 and 8 mEq./L.; and (3) calcium levels remained relatively unchanged (range of approximately 0.5 mEq./L.).

## COMMENTS

In the presence of normal sinus rhythm a slight degree of cardiac slowing is observed with moderate potassium elevation. In advanced stages of potassium intoxication the atrial rate tends to decrease, leading to atrial standstill with the final development of a slow idioventric-

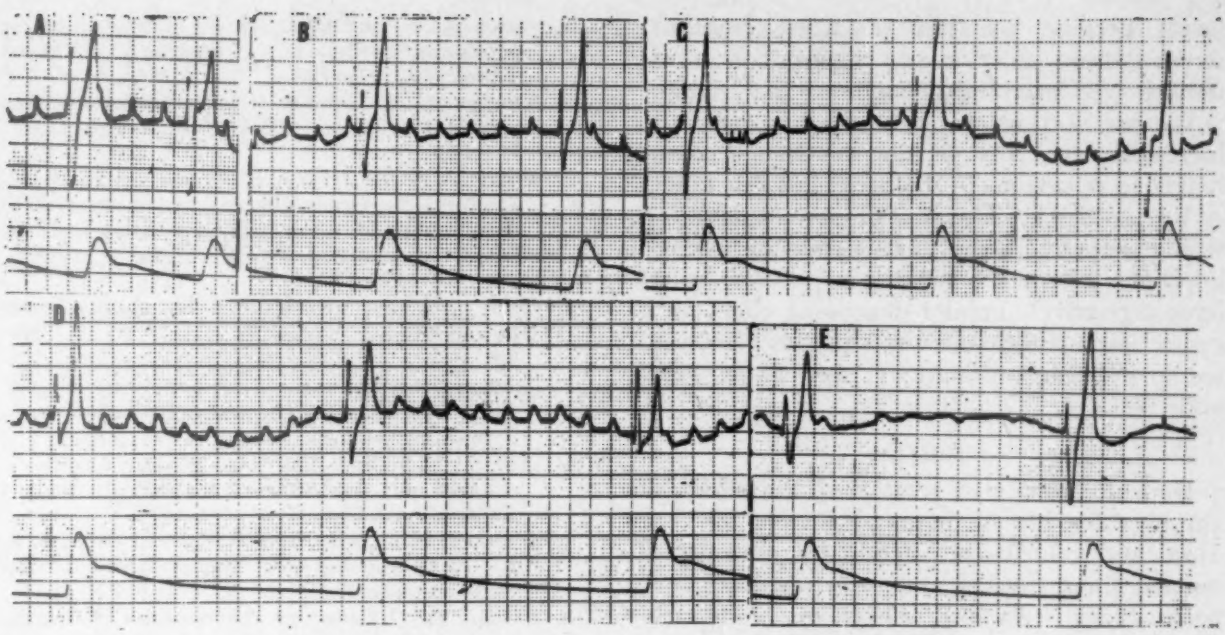



FIG. 4. The effect of potassium infusion in a typical experiment on the atrial and ventricular rate in a dog with complete A-V heart block. (The upper strips represent the electrocardiogram, lead II; the lower strips show the intra-arterial registration of the blood pressure.) *A*, control. The ventricular rate is 55 per minute, the atrial rate is 240 per minute, serum potassium 4.11 mEq./L. Note the widened QRS complexes indicating that the ventricular pacemaker arises from the lower portion of the bundle of His or the upper portion of the interventricular septum. The blood pressure is 107/71 mm. Hg. *B*, following potassium infusion, the serum potassium level has increased to 6.6 mEq./L. Note the decrease in ventricular rate to 32 per minute, whereas the atrial rate does not change significantly. The blood pressure is 117/67 mm. Hg. *C*, serum potassium is increased to 7.55 mEq./L. Note further decrease of ventricular rate to 25 per minute and practically unchanged atrial rate. Blood pressure is 124/67 mm. Hg. *D*, serum potassium is 9.75 mEq./L. The ventricular rate has decreased to 20 per minute. Note the increase in atrial rate to 270 per minute. Blood pressure is 121/63 mm. Hg. *E*, serum potassium is 9.86 mEq./L. The ventricular rate now is 19 per minute; P waves are no longer discernible. (After a short period of fibrillation, there was cessation of atrial activity.) Blood pressure is now 108/59 mm. Hg.

ular rhythm.[2,7,9,11] A comparison in our experiments of the effects observed in the presence of normal sinus rhythm and complete A-V heart block shows that atrial slowing occurs at slightly higher serum potassium levels in the presence of normal sinus rhythm. Otherwise, it may be noted that the changes in atrial rate resemble closely those observed in the presence of complete A-V heart block (Figs. 1, 3 and 4). However, a marked difference is noted in the ventricular response. The ventricular rate in complete A-V heart block decreased 51 per cent with serum potassium levels up to 7.75 mEq./L., a significant drop occurring in most instances already with levels up to 6.5 mEq./L. In most of these cases the resulting rate was below 20 per minute. In the presence of normal sinus rhythm no significant changes in the ventricular rate were observed with serum levels up to 9 and 10 mEq./L. (Figs. 1 and 3) and in the majority of our experiments the ventricular rate remained fairly fast (70 to 90 per minute) even with very high serum potassium levels (11.5 to 15 mEq./L.).

The findings previously mentioned are of significance in indicating the following: (1) the difference in response of the sinus and ventricular pacemaker to hyperpotassemia; and (2) cardiac standstill may be more easily produced at a lesser degree of hyperpotassemia than is observed in the presence of a normal sinus rhythm.

There are many factors that decrease the rhythmicity of the ventricular pacemaker in complete A-V heart block. Recently, it has been shown experimentally and clinically that acidosis is an important cause in depressing this pacemaker.[16,17] Since the ventricular pacemaker in the presence of complete A-V heart block is also quite sensitive to a slight increment in serum potassium, the occurrence of both of these factors would probably have an additive effect in depressing the ventricular rate. In our experiments acidosis was excluded as a causative

factor because the pH remained constant; serum sodium, chloride and calcium concentrations showed insignificant changes.

We are not certain as to the cause for the increased sensitivity of the ventricular pacemaker to potassium in the presence of complete A-V heart block. The most obvious explanation would appear to be that potassium, which depresses pacemaker activity in general, would have a relatively greater depressing effect on a center of diminished automaticity as compared to one of high automaticity, such as the sinus node.

## Summary

Data are presented relative to the effects of varying degrees of hyperpotassemia on the atrial and ventricular rates in the presence of normal sinus rhythm and with complete A-V heart block. In the initial or moderately advanced stages of hyperpotassemia with serum levels up to 9.2 mEq./L. there is only a slight change in the atrial and ventricular rates in the presence of normal sinus rhythm. However, in the presence of complete A-V heart block the ventricular rate shows a decrease of 51 per cent (±3.61 per cent) from the control rate with serum potassium levels up to 7.75 mEq./L. (±0.22 mEq./L.). The possible relationship between these elevated serum potassium levels and the occurrence of Stokes-Adams seizures in patients with complete A-V heart block is discussed.

## References

1. Bellet, S., Gazes, P. C., and Steiger, W. A. The effect of potassium on the electrocardiogram in the normal dog and in dogs with myocardial infarction. *Am. J. M. Sc.*, 220: 237, 1950.
2. Levine, H. D., Merrill, P. and Somerville, W. Advanced disturbances in the cardiac mechanism in potassium poisoning. *Circulation*, 3: 889, 1951.
3. Chamberlain, F. L., Scudder, J. and Zweimer, R. L. Electrocardiographic changes associated with experimental alterations in blood potassium in cats. *Am. Heart J.*, 18: 458, 1939.
4. Crisman, J. M., Crisman, C. S., Calabresi, M. and Darrow, D. C. Electrolyte redistribution in cat heart and skeletal muscle in potassium poisoning. *Am. J. Physiol.*, 139: 667, 1943.
5. Nahum, L. H. and Hoff, H. E. Observations on potassium fibrillation. *J. Pharmacol. & Exper. Therap.*, 65: 322, 1939.
6. Wiggers, C. J. Studies of ventricular fibrillation produced by electric shock. *Am. J. Physiol.*, 93: 197, 1930.
7. Winkler, A. W., Hoff, H. E. and Smith, P. K. Electrocardiographic changes and concentration of potassium on serum following intravenous injection of potassium chloride. *Am. J. Physiol.*, 124: 478, 1938.
8. Finch, C. A. and Marchand, J. F. Cardiac arrest by the action of potassium. *Am. J. M. Sc.*, 206: 507, 1943.
9. Finch, C. A., Sawyer, C. G. and Flynn, J. M. Clinical syndrome of potassium intoxication. *Am. J. Med.*, 1: 337, 1946.
10. Martin, H. E. and Wertman, W. M. Electrolyte changes and the electrocardiogram in diabetic acidosis. *Am. Heart J.*, 34: 646, 1947.
11. Stewart, H. J., Sheppard, E. M., and Horger, E. L. Electrocardiographic manifestations of potassium intoxication. *Am. J. Med.*, 5: 821, 1948.
12. Tarail, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.*, 5: 828, 1948.
13. Bettinger, J. C., Surawicz, B., Bryfogle, J. W., Anderson, B. N. and Bellet, S. The effect of intravenous administration of potassium chloride on ectopic rhythms, ectopic beats and disturbances in A-V conduction. *Am. J. Med.*, 21: 521, 1956.
14. Hudson, J. B., Chobanian, A. V. and Relman, A. S. Hypoaldosteronism. A clinical study of a patient with an isolated adrenal mineralocorticoid deficiency, resulting in hyperkalemia and Stokes-Adams attacks. *New England J. Med.*, 257: 529, 1957.
15. Bellet, S., Wasserman, F. and Brody, J. I. Molar sodium lactate. Its effect in complete A-V heart block and cardiac arrest occurring during Stokes-Adams seizures and in terminal states. *New England J. Med.*, 253: 891, 1955.
16. deLeon, A. C., Jr., Bellet, S. and Muller, O. F. The effect of acidosis and/or hyperpotassemia on idioventricular rate in complete A-V heart block: A clinical study. In preparation.
17. Guzman, S. V., deLeon, A. C., Jr., West, J. and Bellet, S. Cardiac effects of isoproterenol, norepinephrine and epinephrine in complete A-V heart block during experimental acidosis, hyperkalemia and hypoxia. *Circulation Res.*, 7: 666, 1959.
18. Abrams, W. B., Lewis, D. W. and Bellet, S. The effect of acidosis and alkalosis on the plasma potassium concentration and the electrocardiogram of normal and potassium-depleted dogs. *Am. J. M. Sc.*, 222: 506, 1951.

# Review

# Calcium and the Electrocardiogram

## I. The Electrocardiographic Manifestations of Hypoparathyroidism*

DAVID BRONSKY, M.D., ALVIN DUBIN, M.S., SHELDON S. WALDSTEIN, M.D.
*and* DANIEL S. KUSHNER, M.D.

Chicago, Illinois

THE EARLIEST recognized electrocardiographic manifestation of hypocalcemia is prolongation of the Q-Tc interval.[1,2] Abnormalities of the T wave have also been described but are less well documented.[3] It is the purpose of this paper to describe the electrocardiographic changes in the presence of hypocalcemia observed in patients with hypoparathyroidism, with particular reference to abnormalities of the T waves.

### SELECTION OF PATIENTS

Twenty-two patients, nineteen women and three men, with hypoparathyroidism were studied. Their average age was thirty-five years, ranging from eleven to seventy-two years (Table 1). All but two patients were Negro. The diagnosis of hypoparathyroidism was established in each patient by demonstrating the signs and symptoms of tetany, a serum calcium level of less than 7.5 mg. per 100 ml., a serum inorganic phosphorus level above 5 mg. per 100 ml. and the absence of roentgenologic signs of osteomalacia. No patient presented renal insufficiency, alkalosis or steatorrhea. The serum levels of potassium and total protein were within normal limits in all. The etiology of hypoparathyroidism was subtotal thyroidectomy performed for hyperthyroidism in eighteen patients, and total thyroidectomy for carcinoma of the thyroid gland in two patients. The remaining two patients had idiopathic hypoparathyroidism and pseudohypoparathyroidism, respectively. Their detailed histories have been presented elsewhere.[4]

Fourteen patients were studied during the acute stage of tetany from one to eleven days after thyroidectomy. The others presented chronic hypoparathyroidism, defined here as untreated or inadequately treated tetany of one or more years' duration. One patient (Case 10) was studied in both the acute and chronic phase of her illness. Two patients (Cases 7 and 17) had asymptomatic rheumatic heart disease and one (Case 3) had esssential hypertension. An additional patient (Case 4) presented unexplained cardiomegaly and return of heart size to normal with antitetanic treatment. A more complete report of this patient is presented elsewhere.[5] None of the remaining patients presented clinical evidence or had a history of cardiac or pulmonary disease prior to or during the period of study. All the patients were euthyroid when hypoparathyroidism developed and none was receiving digitalis.

### METHODS

Upon establishment of the diagnosis of hypoparathyroid tetany, twelve lead electrocardiograms were obtained in all patients and repeated serially until therapy with dihydrotachysterol, vitamin D and calcium salts restored the serum calcium level to normal limits. At the time of the initial electrocardiograms the serum calcium levels ranged from 5.7 to 8.1 mg. per 100 ml. (Table 1). The acute effect of intravenous infusions of 5 per cent calcium gluconate upon the electrocardiogram was studied in six patients. All the electrocardiograms were taken by one of the authors or trained technicians using the Sanborn Cardiette electrocardiograph. Serum calcium levels were determined by the method of

* From the Hektoen Institute for Medical Research and the Endocrine Clinic of the Cook County Hospital; and the Departments of Medicine of the University of Illinois College of Medicine and Northwestern University Medical School, Chicago, Illinois. These studies were supported in part by a grant from the Dr. Leonard H. and Louis D. Weissman Medical Research Foundation.

TABLE I

The Intervals of the Ventricular Complex and Configuration of the T Waves in Twenty-two Patients with Hypoparathyroidism in the Normocalcemic and Hypocalcemic States

| Case No. | Form of Hypoparathyroidism | Age (yr.) | Serum Calcium (mg./100 m'.) | Intervals (hundredths of second) | | | | | T Waves |
|---|---|---|---|---|---|---|---|---|---|
| | | | | R–R | Q-oTc | Q-aTc | Tc | Q-Tc | |
| 1 | Pseudo | 16 | 10.4 | 92 | 22 | 27 | 15 | 37 | Normal |
| | | | 7.3 | 69 | 36 | 47 | 15 | 51 | Inverted (Fig. 1) |
| 2 | Idiopathic | 11 | 9.5 | 56 | 25 | 37 | 23 | 48 | Normal |
| | | | 5.8 | 66 | 35 | 44 | 20 | 54 | Elevated |
| 3 | Chronic, PO* | 62 | 9.4 | 72 | 27 | 42 | 22 | 49 | Normal |
| | | | 8.1 | 76 | 34 | 51 | 28 | 62 | Normal |
| 4 | Chronic, PO | 41 | 10.4 | 74 | 24 | 33 | 15 | 40 | Normal |
| | | | 7.4 | 58 | 40 | 46 | 14 | 54 | Inverted |
| 5 | Chronic, PO | 29 | N† | 58 | 22 | 35 | 18 | 41 | Normal |
| | | | 7.7 | 60 | 33 | 41 | 19 | 52 | Normal |
| 6 | Chronic, PO | 42 | 9.3 | 44 | 24 | 33 | 15 | 39 | Normal |
| | | | 6.3 | 70 | 36 | 43 | 17 | 53 | Inverted |
| 7 | Chronic, PO | 29 | 9.2 | 74 | 29 | 39 | 23 | 52 | Normal |
| | | | 8.1 | 68 | 33 | 45 | 19 | 52 | Normal |
| 8 | Chronic, PO | 49 | 9.1 | 85 | 26 | 39 | 19 | 46 | Normal |
| | | | 7.3 | 87 | 26 | 39 | 21 | 47 | Inverted |
| 9 | Acute, PO‡ | 72 | 10.0 | 82 | 23 | 38 | 19 | 42 | Normal |
| | | | 7.8 | 81 | 27 | 35 | 18 | 45 | Normal |
| 10 | Acute, PO | 31 | 9.3 | 51 | 28 | 32 | 15 | 44 | Normal |
| | | | 5.7 | 67 | 34 | 48 | 23 | 57 | Elevated |
| 11 | Acute, PO | 50 | 11.0 | 67 | 26 | 33 | 18 | 44 | Normal |
| | | | 7.3 | 51 | 25 | 39 | 24 | 49 | Markedly elevated (Fig. 2) |
| 12 | Acute, PO | 22 | N† | 72 | 26 | 32 | 15 | 41 | Normal |
| | | | 7.4 | 82 | 27 | 38 | 18 | 44 | Normal |
| 13 | Acute, PO | 70 | 12.4 | 64 | 24 | 35 | 17 | 41 | Flat |
| | | | 6.4 | 74 | 35 | 44 | 21 | 56 | Severely inverted |
| 14 | Acute, PO | 23 | 11.8 | 59 | 17 | 23 | 13 | 30 | Inverted (Fig. 6A) |
| | | | 7.4 | 64 | 25 | 40 | 33 | 58 | Normal |
| | | | 6.5 | 100 | 32 | 42 | 18 | 50 | Inverted |
| 15 | Acute, PO | 41 | 11.9 | 52 | 26 | 33 | 19 | 46 | Normal |
| | | | 6.2 | 56 | 32 | 43 | 20 | 52 | Normal |
| 16 | Acute, PO | 41 | N† | 64 | 20 | 35 | 20 | 40 | Normal |
| | | | 7.6 | 69 | 30 | 43 | 18 | 48 | Inverted (Fig. 3) |
| 17 | Acute, PO | 24 | 10.4 | 79 | 22 | 34 | 18 | 40 | Normal |
| | | | 5.8 | 76 | 35 | 46 | 13 | 50 | Inverted (Fig. 4) |
| 18 | Acute, PO | 30 | N† | 62 | 23 | 34 | 19 | 42 | Normal |
| | | | 7.1 | 80 | 27 | 43 | 29 | 56 | Severely inverted (Fig. 5) |
| 19 | Acute, PO | 19 | 10.3 | 70 | 28 | 42 | 18 | 45 | Normal |
| | | | 6.2 | 70 | 33 | 43 | 17 | 50 | Normal |
| 20 | Acute, PO | 26 | 13.1 | 54 | 16 | 24 | 22 | 38 | Normal |
| | | | 8.0 | 74 | 24 | 36 | 21 | 45 | Normal |
| 21 | Acute, PO | 26 | 10.6 | 66 | 21 | 35 | 22 | 43 | Normal |
| | | | 6.3 | 94 | 29 | 37 | 17 | 45 | Flat |
| 22 | Acute, PO | 23 | 9.3 | 59 | 21 | 29 | 22 | 43 | Normal |
| | | | 6.5 | 60 | 32 | 45 | 21 | 53 | Normal |

* Chronic postoperative hypoparathyroidism; i.e., inadequately treated tetany of more than one year's duration.

† Electrocardiogram taken prior to surgery and calcium level assumed normal.

‡ Acute postoperative hypoparathyroidism with onset one to eleven days after surgery.

TABLE II

Summary of the Changes in the Intervals of the Ventricular Complex and Configuration of the T Waves in the Normocalcemic and Hypocalcemic States

| Group | Serum Calcium (mg./100 ml.) | Change in Interval (hundredths of second) | | | | T Waves Inverted |
|---|---|---|---|---|---|---|
| | | Q-oTc | Q-aTc | Tc | Q-Tc | |
| Normocalcemia* | 10.3† (9.1–13.1*) | 24 (16–29) | 34 (24–42) | 19 (15–23) | 43‡ (30–52) | 1 |
| Hypocalcemia | 7.0 (5.7–8.1) | 32 (25–40) | 43 (35–51) | 20 (13–33) | 52 (44–62) | 9 |

* For completeness, the four patients with serum calcium levels above 11 mg./100 ml. were included. Their omission would not have changed the results significantly.

† Mean. Range in parentheses.

‡ This value is within normal limits for women (Bazett, 0.44 second), the sex of nineteen of the twenty-two patients studied.

Kramer and Tisdall.[6] In this laboratory the normal range of serum calcium level is 9 to 11 mg. per 100 ml.

The electrocardiograms during the period of hypocalcemia were compared to those secured prior to the onset of tetany, when available, or to those obtained after recovery. The intervals of the ventricular complex were named and measured by the procedure of Lepeschkin and Surawicz.[7,8] The intervals Q-oTc, Q-aTc and Q-Tc refer respectively to the origin, apex and end of the T wave as measured from the Q deflection, and the symbol Tc denotes the duration of the T wave as corrected for heart rate by Bazett's formula as follows:

$$Q - Tc = \frac{Q - T}{\sqrt{R - R}}$$

The durations of these intervals are listed in Table I.

## RESULTS

*Heart Rate, Rhythm, P-R and QRS Intervals:* No correlation was observed between the heart rate and the serum calcium level. Sinus arrhythmia was observed in the two youngest patients and one patient had frequent ventricular extrasystoles both before and after treatment. All other patients had a normal sinus rhythm. The duration and configuration of the P-R interval, the P wave and the QRS interval were within normal limits in all cases and were unaffected by the fall in the level of serum calcium. Bundle branch block was not observed. Changes in the magnitude of the R and S waves occurred inconsistently without relationship to changes in the level of serum calcium.

*The Q-Tc Interval:* Prolongation of the Q-T interval as corrected for heart rate during hypocalcemia was observed in all but one case (Case 7) and was slight in two cases (Cases 8 and 21). The degree of prolongation was otherwise inversely proportional to the serum calcium level.[10] The average Q-Tc interval during hypocalcemia was 0.52 second and the range was 0.44 to 0.62 second. When the serum calcium level was restored to normal the average Q-Tc interval was 0.43 second and the range was 0.30 to 0.52 second (Table II). These values are within normal limits for women, who comprise the majority of patients studied.[11] The ratio during hypocalcemia of the observed Q-T interval to that predicted for the given heart rate by Bazett's formula[9] (Q-T = $0.40\sqrt{\text{R-R}}$ for women, $0.47\sqrt{\text{R-R}}$ for men) was 1.29 and the range was 1.11 to 1.53.

*The Q-oTc segment.* The segment from the Q wave deflection to the onset of the T wave when corrected for heart rate was prolonged in all but three patients (Cases 8, 11 and 12) and, like the Q-Tc interval, was inversely proportional to the serum calcium level.[10] The mean Q-oTc during hypocalcemia was 0.32 second and the range was 0.16 to 0.40 second. When normocalcemia was restored the mean was 0.24 second and range 0.16 to 0.29 second (Table II). Deviation of the S-T segment from the isoelectric position was not observed.

*The Q-aTc segment.* The measurement from the Q wave deflection to the apex of the T wave is subject to less error of determination than the Q-oTc segment. The changes observed were of the same order as those described for the Q-oTc (Table II). A shift of the apex

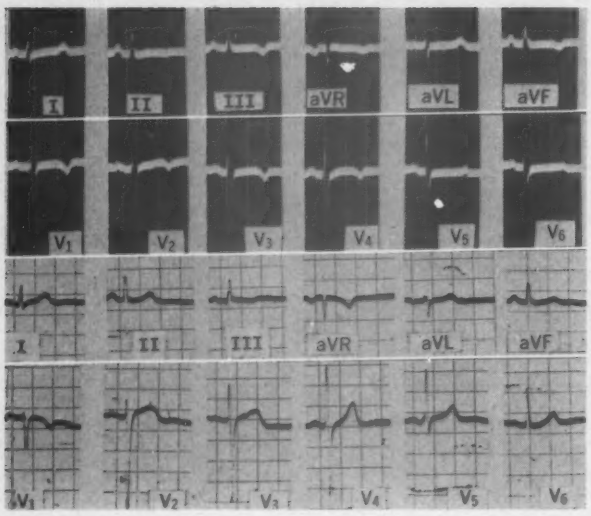



FIG. 1. (Case 1.) Pseudohypoparathyroidism.[4] *Above*, electrocardiogram taken on admission, serum calcium 7.3 mg. per 100 ml. *Below*, several weeks after institution of therapy, serum calcium is 10.4 mg. per 100 ml. The T wave inversion in leads $V_1$-$V_4$ were considered consistent with a juvenile pattern in this sixteen year old girl until their reversal was observed.

toward the end of the Q-T interval was often observed during tetany.

*The Tc segment.* The duration of the T wave as corrected for heart rate was usually unaffected by a fall in the serum calcium level[10] (Table II). In two patients, however, marked prolongation of the Tc was observed (Fig. 5, 6).

*T Wave Abnormalities:* In all patients, the configuration of the T waves during hypocalcemia differed from that observed when normocalcemia was restored. In nine, the changes were minimal, consisting of a slight elevation and peaking of the T wave with a tendency of the apex to be displaced toward the end of the Q-T interval. In Table I, these are listed as normal T waves. Definite elevations of the T wave occurred in three patients. The greatest elevation observed is illustrated in Figure 2. In nine patients sharp, symmetrical, late inversions of the T waves were observed. These inversions were prominent in leads from the right side of the precordium. T wave changes in the standard limb leads from these patients were sometimes slight in comparison. In two patients the T wave inversions were so extensive and severe as to suggest the possibility of a myocardial infarction (Fig. 5). In one patient flattening of the T waves without actual inversion was noted. The type and magnitude of abnormalities of the T wave observed in the electrocardiogram of patients with hypo-

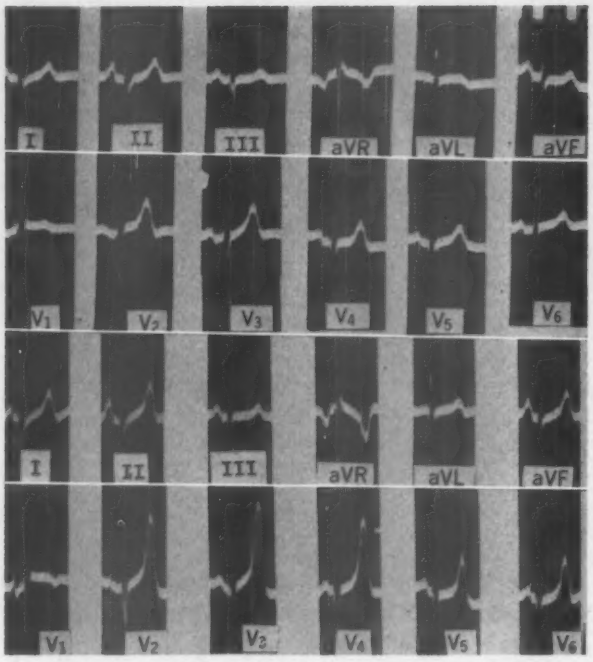



FIG. 2. (Case 11.) Acute postoperative hypoparathyroidism. *Above*, electrocardiogram prior to thyroidectomy, serum calcium 11 mg. per 100 ml. *Below*, electrocardiogram eight days after surgery, serum calcium 7.3 mg. per 100 ml. The marked elevation and tenting of the T waves particularly in leads $V_2$-$V_4$ suggested hyperkalemia. The serum potassium, however, was normal. With antitetanic therapy, the T waves reverted gradually to their normal configuration.

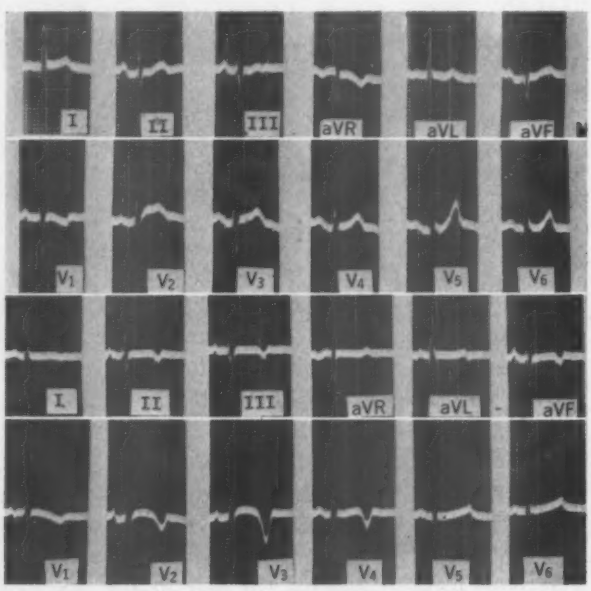



FIG. 3. (Case 16.) Acute postoperative hypoparathyroidism with asymptomatic rheumatic heart disease. *Above*, electrocardiogram prior to surgery, serum calcium presumed normal. *Below*, electrocardiogram eight days after surgery, serum calcium 7.6 mg. per 100 ml. The T wave inversions suggested an acute right heart strain pattern. There was no clinical evidence to support this diagnosis, however, and the electrocardiogram became normal upon spontaneous recovery from the tetany.

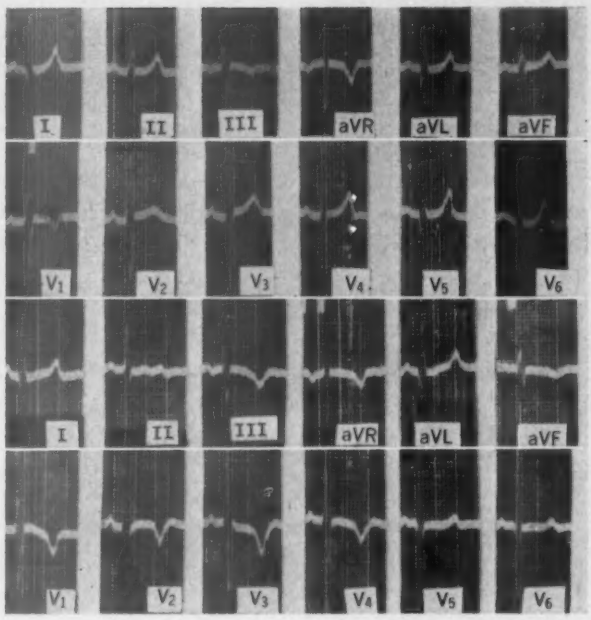



FIG. 4. (Case 17.) Acute postoperative hypoparathyroidism. Normal heart. *Above*, electrocardiogram prior to surgery, serum calcium 10.4 mg. per 100 ml. *Below*, three days after surgery, serum calcium 5.8 mg. per 100 ml. With antitetanic therapy, the T waves gradually reverted to their normal configuration.

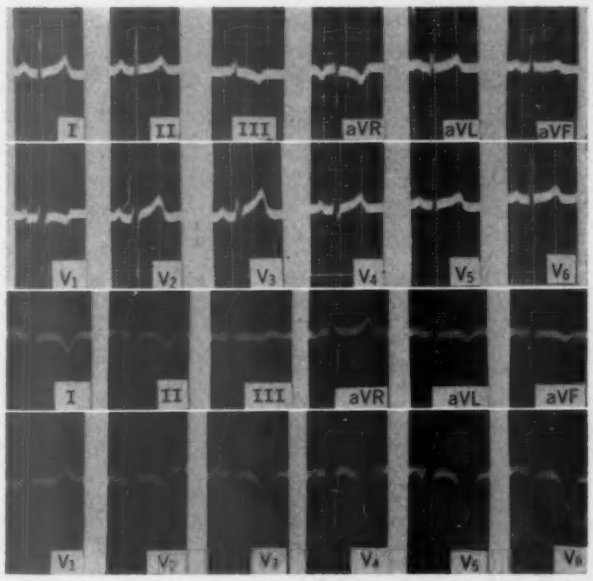



FIG. 5. (Case 18.) Acute postoperative hypoparathyroidism. *Above*, electrocardiogram prior to surgery, serum calcium presumed normal. *Below*, electrocardiogram six days after surgery, serum calcium 7.1 mg. per 100 ml. The severe generalized T wave inversions suggested a myocardial infarction. However, there was no clinical evidence to support that diagnosis in this thirty year old woman. The T waves did not become upright until several weeks after the serum calcium returned to normal with antitetanic therapy.

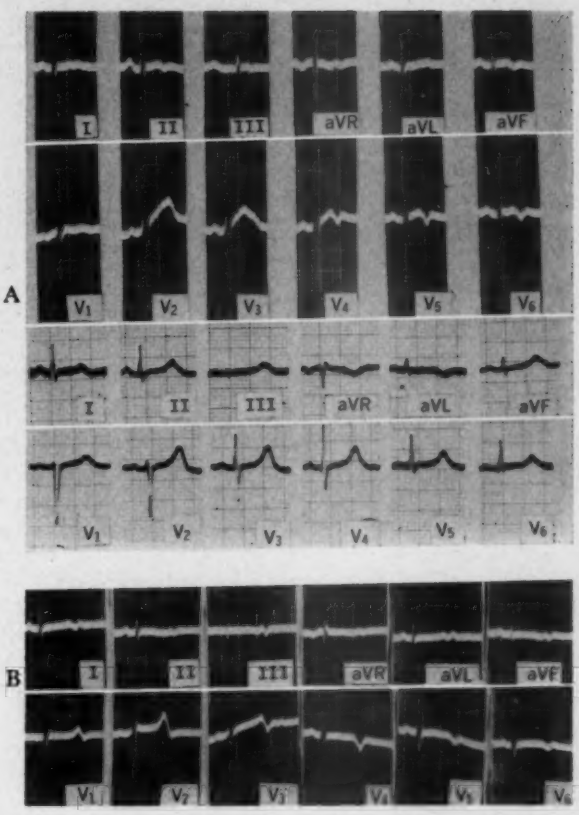



FIG. 6. (Case 14.) Acute postoperative hypoparathyroidism. *A*, *Above*, electrocardiogram prior to thyroidectomy, serum calcium level 11.8 mg. per 100 ml. T wave inversions were attributed to hyperthyroidism.[32] *Below*, electrocardiogram taken three days after surgery, serum calcium 7.4 mg. per 100 ml. T waves are now upright. Note long Tc duration. It is probable that had an electrocardiogram been obtained when the patient was euthyroid prior to thyroidectomy the T wave inversions would have been corrected. *B*, six months later, serum calcium was 7.2 mg. per 100 ml. The patient had inadvertently discontinued medication and tetanic convulsions necessitated rehospitalization. T wave inversions characteristic of tetany are now present. With restoration of a normal serum calcium level, the electrocardiogram became normal.

parathyroidism are illustrated in Figures 1 through 6.

The abnormalities of the T waves observed had no relationship to either the cause or the duration of tetany. T wave inversion was observed in a patient with pseudohypoparathyroidism while elevation occurred in a patient with idiopathic hypoparathyroidism. Inversions were observed in six patients with acute, and in three patients with chronic, postoperative hypoparathyroidism. Three other patients presenting chronic postoperative hypoparathyroidism, including a patient with tetany of twenty years' duration, did not show this abnormality. Elevation of the T waves was

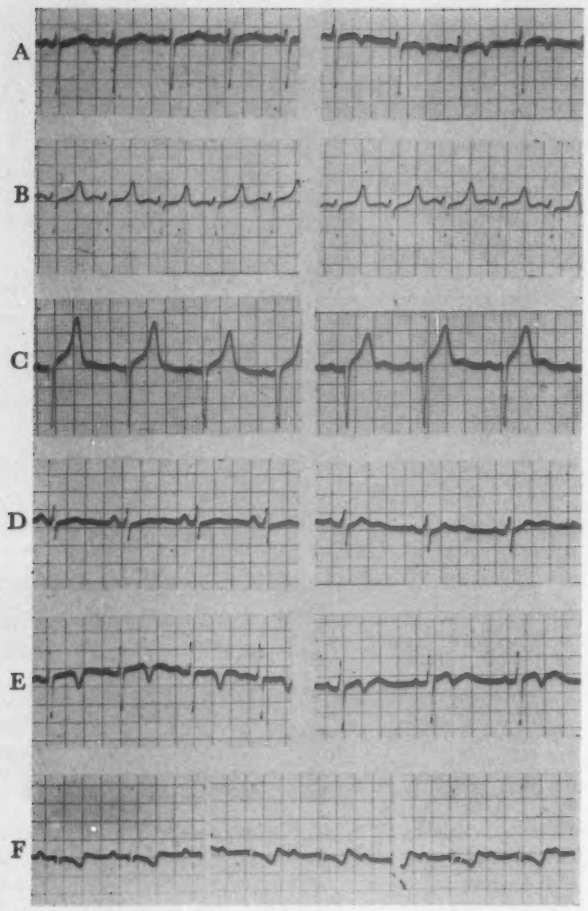



FIG. 7. Effect of intravenous 5 per cent calcium gluconate on the electrocardiogram. *A*, acute postoperative tetany (Case 10, serum calcium 6.5 mg. per 100 ml., lead $V_3$). Note inversions of T waves after 20 cc. solution was infused in two minutes. *B*, same patient after one and a half years of chronic tetany (serum calcium was 6.2 mg. per 100 ml., lead $V_3$). Note the tall peaked T waves now present. After 160 cc. solution was infused in three hours, the calcium rose to 9.7 mg. per 100 ml. with slight effect upon the electrocardiogram. *C*, acute postoperative tetany (Case 11, serum calcium 8.2 mg. per 100 ml., lead $V_2$). Same patient as in Figure 2. After 180 cc. of solution was infused in three hours, the calcium rose to 11.5 mg. per 100 ml. Note the slight decrease in amplitude of the T wave and appearance of prominent U waves as the Q-T interval became shorter. *D*, acute postoperative tetany (Case 16, serum calcium 8.3 mg. per 100 ml., lead II). Same patient as in Figure 3. After 20 cc. of solution was infused in five minutes, note the shortening of Q-T interval, increased amplitude of T wave and appearance of prominent U waves. *E*, same patient, lead $V_3$. Note decrease in depth of T wave inversion after infusion of calcium. *F*, effect of acute infusion of calcium in a hypocalcemic, digitalized, uremic patient without hypoparathyroidism. Note increasing A-V block (see text).

observed in one patient each with acute and chronic postoperative hypoparathyroidism. In three patients the initial electrocardiogram at the onset of tetany showed no T wave changes, but inversion occurred within one week in two and after six months in the third (Fig. 6A). Two patients presented inversions of the T waves when hyperthyroid. In one (Case 15) the T waves became normal when the patient became euthyroid prior to surgery and remained upright when tetany developed. The other patient is described in Figure 6. Both of the patients with asymptomatic mitral stenosis exhibited T wave inversions. In one, however, the T wave polarity varied from week to week, regardless of the serum calcium level. Similar instances of T wave instability have been described by Ljung.[3]

The appearance of T wave abnormalities had no relationship to either the absolute or relative degree of prolongation of the Q-oTc segment or to the decrement in the level of serum calcium. There was no obvious explanation as to why the polarity of the abnormal T waves varied as they did.

In all patients the configuration of the T wave returned to normal when the serum calcium level became normal with successful antitetanic therapy. In general, the duration of the Q-oTc segment, the configuration of the T wave and the level of serum calcium became normal simultaneously. However, in the two patients with severe T wave inversions, normalization was delayed two and three weeks.

*The U Wave:* Discrete U waves were not observed during tetany in any patient. In two patients U waves, observed during normocalcemia, disappeared when tetany developed. In four patients U waves first appeared after successful antitetanic therapy. The administration of calcium infusions during tetany elicited the appearance of U waves in five of six patients (see the following).

*Acute Effects of Intravenous Calcium:* The intravenous injection of 5 per cent calcium gluconate secured a prompt restoration of a normal Q-oTc and Q-Tc interval in all six patients studied (Fig. 7). A slight decrease in the height of the upright T waves or a slight lessening of the depth of inverted T waves was observed. In no instance, however, did an abnormal T wave revert to normal. In five patients, a prominent U wave appeared in its usual position upon the infusion of calcium. In Case 10, rapid injection of the solution produced a tachycardia and transient inversion of the T waves (Fig. 7A). A slow injection, however, caused a pronounced bradycardia in this and the other patients.

It would be amiss to discuss the effects of intravenous calcium infusions without mentioning the danger of its administration to the digitalized patient. Figure 7F illustrates the effect of intravenous calcium in a uremic patient with chronic glomerulonephritis and hypocalcemia who had been previously digitalized. The marked A-V heart block induced was reversed immediately upon stopping the infusion. Attention is called to the fact that the block was produced by raising the calcium level toward normal and not above it. We have not observed this type of block in the undigitalized patient with hypocalcemia.

*The Electrocardiogram in Hypocalcemia from Etiologies other than Hypoparathyroidism:* Examination of the electrocardiograms of five patients with hypocalcemic tetany from steatorrhea associated with chronic pancreatitis and idiopathic sprue revealed prolongation of the Q-oTc and Q-Tc intervals only. Abnormalities of the T wave were not observed. Hypocalcemia in these patients is accompanied by hypophosphatemia rather than hyperphosphatemia, as found in hypoparathyroidism. To our knowledge, however, serum phosphorus does not affect the electrocardiogram. Abnormalities of the T wave in patients with hypocalcemia accompanying uremia from renal disease have been observed frequently but are usually of the type observed in left ventricular hypertrophy and do not resemble those observed in hypoparathyroid tetany. The present study was limited to patients with hypoparathyroidism because they are the least likely to possess other electrolyte abnormalities or organic disease independently affecting the electrocardiogram.

## Comments

The literature concerning the electrocardiogram in hypoparathyroidism consists of reports of a few small series of cases and isolated case reports.[3,4,12–25] Ljung[3] was the earliest author to stress abnormalities of the T waves. He reported eighteen patients with uncomplicated postoperative hypoparathyroidism. Abnormalities of the T waves, consisting of a slight decrease in amplitude, were observed in eleven patients. Only two patients had actual inversions of the T waves. Four patients exhibited instability of T wave polarity. In his review of the literature prior to 1949, Ljung found only occasional references to T wave abnormalities in hypoparathyroidism. His study and earlier reports utilized only the standard limb leads. For proper evaluation of the effects of hypocalcemia, these leads appear to be inadequate since the present study demonstrates that the major changes are best observed in the precordial leads. Reynolds et al.[20] included six patients with hypoparathyroidism in a report of the electrocardiograms of thirty-one patients with hypocalcemia from various etiologies. Only three patients in his series showed sharp, late inversions of the T waves. Interestingly, all three were patients with hypoparathyroidism. They have since observed a fourth such case. In two patients, the T waves became upright when the serum calcium level was restored to normal by dihydrotachysterol. The effect of intravenous calcium was not studied.[21] Yu[24] reported two patients with hypoparathyroidism. The illustrated electrocardiogram of one of these patients shows sharp, late inversions of the T wave in the right precordial leads similar to those of Figures 4 and 5 of this paper. Similar abnormalities of the T waves have been described by others.[12,13,15,22]

The present study demonstrates that marked abnormalities of the T waves in hypoparathyroidism are more frequent and varied in type than previously reported. The decrement in the serum calcium does not affect the duration of the QRS interval and seldom affects the duration of the T wave segment of the Q-T interval. The prolongation of the Q-Tc interval, therefore, can usually be attributed entirely to the increase in duration of the S-T segment.[10,24] Lowering the serum calcium level has no effect on cardiac rhythm but may, under special circumstances (see the following), increase the heart rate. The duration of the P-R interval also remains unaffected. Lastly, the contour and the time of appearance of the U wave in hypocalcemia is normal but becomes obscured by the delay in the termination of the T wave. This is unlike hypokalemia when the U wave becomes prominent and encroaches upon the T wave.[25]

*Induced Hypocalcemia with EDTA:* The effect of lowering the serum calcium level with the calcium chelating agent sodium ethylenediamine tetraacetic acid (NaEDTA) has been studied recently in both man and animals. Bechtel et al.[26] administered NaEDTA for thirty minutes to five normal men and successfully lowered the serum calcium to tetany levels. They observed an increase in the heart rate and prolongation of the Q-oTc and thereby the Q-Tc interval, inversely pro-

portional to the degree of induced hypocalcemia. A slight reduction in the amplitude of the T waves was also observed. In experiments on animals, longer periods of induced hypocalcemia have produced greater changes in the T waves. Kleinfeld and Gross[27] induced severe, prolonged hypocalcemia in rabbits with Na-EDTA. Many of their animals died in tetany. The most consistent abnormalities produced were prolongation of the Q-Tc interval, due to lengthening of the S-T segment, and a tall peaked T wave. The amplitude of the T waves sometimes decreased as the serum calcium was further lowered and in six experiments sharp, late inversions of the T waves were observed. Their illustrations of both elevated and inverted T waves in the electrocardiogram of the rabbit during induced hypocalcemia are strikingly similar to those observed in man in this study. Page and Real[28] in a comparable experiment using dogs obtained similar results including "variable changes in the T waves."

*Cause of T Wave Abnormalities:* The cause of T wave changes associated with hypocalcemia in hypoparathyroidism is not clear. It is particularly difficult to understand why the polarity of the T waves should be altered in either direction in normal hearts from presumably the same cause. Marzahn[12,13] ascribed the T wave changes to a myocardial lesion from anoxemia occurring during the period of prolonged systole. Patients with tetany may show arterial spasm particularly in response to epinephrine[4] and it has been suggested that spasm of the coronary arteries may account for the abnormal T waves.[3] Ljung[3] postulated that a functional disturbance of the myocardium was responsible for the abnormal T wave patterns.

*Cause of S-T Prolongation:* The prolongation of the S-T segment in hypocalcemia is usually associated with prolongation of mechanical systole[25] and has been attributed to specific alterations in the shape of the action potentials recorded from single ventricular myocardial fibers.[29] Surawicz et al.[29] have studied the simultaneously obtained monophasic action potentials, electrocardiograms and ventricular pressures of isolated rabbit hearts perfused by calcium-free solutions. Prolongation of the Q-oT segment of the electrocardiogram was accompanied by simultaneous widening of the plateau phase of the action potential and a decrease in the force of contraction. After forty to seventy-five seconds, the action potential plateau gradually shortened and, at this point, the duration of the S-T segment also shortened and the T waves inverted. Administration of a calcium-containing solution effected prompt recovery. In the present study, however, we found no correlation between the degree of prolongation of the Q-oTc segment and the polarity of the T wave.

*Calcium and Myocardial Repolarization:* Calcium ions apparently affect a link between the process of depolarization and contraction of cardiac muscle fibers in that order.[30] This sequence depends in part upon an effect of calcium ions on the electrical stability of the surface membranes of the muscle fibers influencing the magnitude, range and duration of potassium and sodium exchanges.[28] In addition, there is evidence that a portion of calcium ions are taken up reversibly by a superficial layer of heart tissue and may influence the activation of cardiac contraction.[31]

This study of the electrocardiographic manifestation of hypocalcemia from hypoparathyroidism demonstrates two types of abnormalities, both localized to the repolarization phase of the ventricular complex. The first abnormality is a consistent prolongation of the Q-oTc segment, and thereby the Q-Tc interval, inversely proportional to the serum calcium level. The duration of the T wave segment is, in general, not affected. This effect is perhaps related to the role of calcium ions upon cell membrane permeability for it is promptly reversed by giving calcium solutions. The second abnormality is a change in the contour and polarity of the T wave, usually minimal, often showing a sharp late inversion and occasionally showing a marked elevation. This effect is inconstant and without a direct relationship to the serum calcium level. It is not fully corrected by acute infusions of calcium solutions but is corrected by a more gradual restoration of serum calcium levels. This suggests that it may be due to organic calcium acting upon the contracting substance of the myocardium. It is not clear why the polarity of the T wave may vary in either direction.

## Summary

The electrocardiograms of twenty-two patients with hypoparathyroidism were examined during hypocalcemia and compared to those obtained when normocalcemia was restored. Prolongation of the Q-oTc segment causing, thereby, prolongation of the Q-Tc interval

was observed in almost all cases and the degree of prolongation was inversely proportional to the level of serum calcium. The duration of the T wave segment in general was unchanged.

Changes in the contour of the T waves were observed in all patients. In nine patients these were slight and consisted only of slight elevation, peaking and displacement of the apex to the end of the Q-T interval; in nine patients the T waves showed sharp, late inversions; in one, the T waves were flattened; and in three, tall, peaked T waves were observed. These changes were most pronounced in the right precordial leads. They were observed in all forms of both acute and chronic tetany due to hypoparathyroidism.

Upon gradual restoration of the normal serum calcium level by appropriate antitetanic therapy, all electrocardiographic abnormalities were eliminated. Acute infusions of intravenous calcium during the hypocalcemic period, however, achieved only shortening of the Q-oTc and hence the Q-Tc intervals, but had only minor effects on abnormalities of the T wave. This suggests that hypoparathyroid hypocalcemia may produce two distinct effects on the myocardium. One, related to ionic calcium and the permeability of the cell membrane, is responsible for the increased duration of the repolarization phase of the ventricular complex. The other, perhaps related to organic calcium and the contractile substance of the myocardium, inconstantly affects the configuration of the T wave, often causing variations in its polarity.

## Acknowledgment

We are indebted to Dr. Luke R. Pascale for his initial studies of Cases 3 and 8.

## References

1. Carter, E. P. and Andrus, C. QT interval in human electrocardiogram in absence of cardiac disease. *J. A. M. A.*, 78: 1922, 1922.
2. White, P. P. and Mudd, S. G. Observations on the effect of various factors on the duration of the electrical systole of the heart as indicated by the length of the QT interval of the electrocardiogram. *J. Clin. Invest.*, 7: 387, 1929.
3. Ljung, O. The electrocardiogram in hypocalcemia with special reference to the T wave. *Acta med. Scandinav.*, 136: 56, 1949.
4. Bronsky, D., Kushner, D. S., Dubin, A. and Snapper, I. Idiopathic hypoparathyroidism and pseudohypoparathyroidism: case reports and review of the literature. *Medicine*, 37: 317, 1958.
5. Bronsky, D., Slodki, S. J., Dubin, A., Emmanuel, R. and Kushner, D. S. The natural history of chronic hypoparathyroidism. In preparation.
6. Kramer, B. and Tisdall, F. F. The direct quantitative determinations of sodium, potassium, calcium, and magnesium in small amounts of blood. *J. Biol. Chem.*, 48: 223, 1921.
7. Lepeschkin, E. and Surawicz, B. The measurement of the Q-T interval of the electrocardiogram. *Circulation*, 6: 378, 1952.
8. Lepeschkin, E. and Surawicz, B. The duration of the Q-U interval and its components in electrocardiograms of normal persons. *Am. Heart J.*, 46: 9, 1953.
9. Bazett, H. C. An analysis of the time relations of the electrocardiogram. *Heart*, 7: 353, 1918.
10. Bronsky, D., Dubin, A., Kushner, D. S. and Waldstein, S. S. Calcium and the electrocardiogram. III. The relationship of the intervals of the electrocardiogram to the level of serum calcium. *Am. J. Cardiol.*, 7: 840, 1961.
11. Kossmann, C. E. The normal electrocardiogram. *Circulation*, 8: 920, 1953.
12. Marzahn, H. Über eine Veränderung des S-T Intervalls im Elektrokardiogramm bei einem Fall von postoperativer Tetanie. *Ztschr. klin. Med.*, 127: 182, 1934.
13. Marzahn, H. Über elektrokardiographische Veränderungen bei postoperativer Tetanie. *Deutsche med. Wchnschr.*, 61: 507, 1936.
14. Hegglin, R. and Holzmann, M. Die klinische Bedeutung der verlängerten QT-Distanz (Systolendauer) in Elektrokardiogramm. *Ztschr. klin. Med.*, 132: 1, 1937.
15. Fernbach, J. and Szandany, Z. Mit Hilfe des Elektrokardiogrammes Diagnostizierte tetanoide Epilepsie. *Klin. Wchnschr.*, 19: 372, 1940.
16. Barker, P. S., Johnstone, F. and Wilson, F. N. The duration of systole in hypocalcemia. *Am. Heart J.*, 14: 82, 1937.
17. Ernstene, A. C. and Proudfit, W. L. Differentiation of the changes in the Q-T interval in hypocalcemia and hypopotassemia. *Am. Heart J.*, 38: 260, 1949.
18. Katz, L. Electrocardiography, p. 451. Philadelphia, 1946. Lea & Febiger.
19. Holzmann, M. Klinische Elektrokardiographie. Stuttgart, 1947. Thieme.
20. Reynolds, T. B., Martin, H. E. and Homann, R. E. Serum electrolytes and the electrocardiogram. *Am. Heart J.*, 42: 671, 1951.
21. Reynolds, T. B. Personal communication.
22. Bellet, S. The electrocardiogram in electrolyte imbalance. *Arch. Int. Med.*, 96: 618, 1955.
23. Jesserer, H. and Tölk, R. Das Elektrokardiogramm bei der Tetanie erwachsener. *Ztschr. Kreislaufforsch.*, 42: 13, 1953.
24. Yu, P. N. G. The electrocardiographic changes associated with hypercalcemia and hypocalcemia. *Am. J. M. Sc.*, 224: 413, 1952.
25. Surawicz, B. and Lepeschkin, E. The electrocardiographic pattern of hypopotassemia with and without hypocalcemia. *Circulation*, 8: 801, 1953.
26. Bechtel, J. T., White, J. E. and Estes, E. H., Jr. The electrocardiographic effects of hypocalcemia induced in normal subjects with Edathamil disodium. *Circulation*, 13: 837, 1956.
27. Kleinfeld, M. and Gross, M. Electrocardio-

graphic manifestations of hypocalcemia produced with ethylenediamine tetraacetic acid. *Am. J. Physiol.*, 187: 479, 1956.

28. Page, E. and Real, J. D. Interrelationship between cardiac effects of ouabain, hypocalcemia and hyperkalemia. *Circulation Res.*, 3: 501, 1955.
29. Surawicz, B., Lepeschkin, E., Herrlich, H. C. and Hoffman, B. F. Effect of potassium and calcium deficiency on the monophasic action potential, electrocardiogram and contractility of isolated rabbit hearts. *Am. J. Physiol.*, 196: 1302, 1959.
30. Niedergerke, R. The potassium chloride contracture of the heart and its modification by calcium. *J. Physiol.*, 134: 584, 1956.
31. Niedergerke, R. The rate of action of calcium ions on the contraction of the heart. *J. Physiol.*, 138: 506, 1957.
32. Sandler, G. The effect of thyrotoxicosis on the electrocardiogram. *Brit. Heart J.*, 21: 111, 1959.

# Calcium and the Electrocardiogram

## II. The Electrocardiographic Manifestations of Hyperparathyroidism and of Marked Hypercalcemia from Various Other Etiologies*

DAVID BRONSKY, M.D., ALVIN DUBIN, M.S., SHELDON S. WALDSTEIN, M.D.
*and* DANIEL S. KUSHNER, M.D.

Chicago, Illinois

THE MOST COMMONLY reported electrocardiographic manifestation of hypercalcemia is shortening of the Q-Tc interval.[1,2] Prolongation of the P-R interval[3] and changes in the configuration of the T waves have also been described.[4,5] It is the purpose of this paper to describe the electrocardiographic manifestations of hyperparathyroidism and of marked hypercalcemia from various other etiologies.

### SELECTION OF PATIENTS

Twelve women with hyperparathyroidism were studied. The patients' ages ranged from thirty to seventy years; the mean was forty-eight years. Four were white and eight Negro. The diagnosis in all but one patient was verified by surgical demonstration of one or more parathyroid adenomas (Table I). The exception (Case 9) was a sixty-eight year old woman with huge, bilateral staghorn renal calculi and biochemical findings of hyperparathyroidism. Surgery was deferred because of moderate renal insufficiency in this patient. All but one patient had hypercalcemia ranging from 12.4 to 16 mg. per 100 ml. The exception (Case 12) had azotemia and a normal serum calcium and phosphorus level when studied. Two patients presented osteitis fibrosa cystica; eight, renal calculus disease; and two, only the biochemical syndrome of hyperparathyroidism (Table I). Other than two patients who presented left ventricular hypertrophy and one who showed right bundle block and atrial fibrillation, none had evidence of cardiac disease and none received digitalis.

Thirteen men and ten women with marked hypercalcemia from various etiologies other than hyperparathyroidism were also studied. The patients' ages ranged from nineteen to eighty years; the mean was fifty-seven years. Fifteen were Negro; seven, white and one, Japanese. The serum calcium level was above 15.5 mg. per 100 ml. in all and between 17 and 24 mg. per 100 ml. in fifteen (Table II). The etiology of hypercalcema was metastatic invasion of bone from carcinoma in eighteen, Hodgkin's disease in one and multiple myeloma in four. These patients were critically ill and most died less than a week after study. Two patients had slight cardiac enlargement; one was in mild congestive heart failure; and nine had severe anemia. One patient (Case 14) was receiving digitalis. In association with marked hypercalcemia, mental confusion, muscular weakness, anorexia, dehydration, vomiting and slight azotemia often were observed.

### METHODS

Serial electrocardiograms were obtained following resection of an adenoma in the patients with hyperparathyroidism. Transient tetany subsequently developed in two patients and a third patient with azotemia had a fall of her serum calcium level. Thus, it was possible to compare the electrocardiogram during hypercalcemia with that of normocalcemia in nine patients and with that of hypocalcemia in three. No electrocardiograms were available in the patients with marked hypercalcemia from other causes when their serum calcium level was within normal limits. The method of recording and measuring the intervals of the electrocardiograms have been presented in the preceding paper.[6]

### RESULTS

*Heart Rate and Rhythm:* No correlation was observed between heart rate and serum calcium

* From the Hektoen Institute for Medical Research and the Endocrine Clinic of the Cook County Hospital; and the Departments of Medicine of the University of Illinois College of Medicine and Northwestern University Medical School, Chicago, Illinois. These studies were supported in part by a grant from the Dr. Leonard H. and Louis D. Weissman Medical Research Foundation.

TABLE I

The Intervals of the Ventricular Complex in Twelve Women with Hyperparathyroidism*

| Case No. | Associated Diagnoses | Age (yr.) | Serum Calcium (mg./100 ml.) | Intervals (hundredths of second) | | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | R-R′ | P-R | Q-oTc | Q-aTc | Tc | Q-Tc | |
| 1 | Ureteral calculus | 43 | 16.0 | 64 | 19 | 20 | 33 | 16 | 36 | |
| | | | 9.4 | 64 | 17 | 26 | 40 | 19 | 45 | |
| 2 | Osteitis fibrosa cystica | 34 | 15.0 | 72 | 19 | 19 | 31 | 20 | 39 | Transient postoperative tetany (Fig. 1) |
| | | | 10.9 | 53 | 16 | 19 | 33 | 23 | 43 | |
| | | | 8.0 | 68 | 16 | 28 | 38 | 18 | 46 | |
| 3 | Nodular goiter | 43 | 14.5 | 92 | 21 | 22 | 31 | 14 | 35 | T wave inversions during transient postoperative tetany |
| | | | 9.8 | 63 | 19 | 24 | 35 | 18 | 44 | |
| | | | 8.1 | 78 | 17 | 27 | 36 | 15 | 42 | |
| 4 | Renal calculi | 60 | 14.2 | 80 | 18 | 16 | 28 | 22 | 38 | |
| 5 | Epilepsy | 32 | 13.8 | 84 | 17 | 18 | 30 | 18 | 36 | |
| | | | 10.8 | 74 | 16 | 22 | 30 | 17 | 40 | |
| 6 | Renal calculi | 33 | 13.6 | 54 | 18 | 16 | 24 | 22 | 38 | |
| | | | 9.5 | 70 | 18 | 24 | 30 | 17 | 41 | |
| 7 | Bladder calculus | 54 | 13.3 | 78 | 17 | 23 | 32 | 18 | 41 | |
| | | | 10.5 | 90 | 16 | 20 | 30 | 20 | 40 | |
| 8 | Arteriosclerotic heart disease | 70 | 13.2 | 63 | ... | 15 | 21 | 15 | 30 | Right bundle branch block, atrial fibrillation |
| | | | 9.5 | 85 | ... | 21 | 28 | 16 | 37 | |
| 9 | Renal calculi | 68 | 12.8 | 80 | 20 | 18 | 31 | 21 | 39 | |
| 10 | Renal calculi | 30 | 12.8 | 60 | 16 | 21 | 26 | 13 | 34 | |
| | | | 10.1 | 70 | 16 | 21 | 28 | 15 | 36 | |
| 11 | Renal calculi, hypertension | 53 | 12.4 | 47 | 14 | 25 | 35 | 16 | 41 | Left ventricular hypertrophy |
| | | | 10.3 | 84 | 16 | 33 | 44 | 20 | 53 | |
| 12 | Osteitis fibrosa cystica, azotemia | 60 | 10.3 | 88 | 18 | 20 | 29 | 21 | 41 | Left ventricular hypertrophy |
| | | | 6.6 | 55 | 18 | 23 | 29 | 23 | 46 | |

* Cases 2 and 3 had transient postoperative tetany and Case 12 with azotemia had a normal serum calcium level before and a low level after surgery.

level. The tachycardia observed frequently in the patients with severe hypercalcemia could be attributed to their associated illnesses. One patient with hyperparathyroidism had atrial fibrillation. One patient with marked hypercalcemia had occasional atrial and ventricular extrasystoles. All other patients had a normal sinus rhythm.

*P-R Interval:* Two patients with hyperparathyroidism had first degree heart block. In one the P-R interval was 0.21 second and became 0.19 second when normocalcemia was restored. During transient tetany, however, the P-R interval shortened further to 0.17 second (Case 3). The other patient has not had surgery. In five patients, the P-R interval was within normal limits prior to surgery but became shorter by 0.01 to 0.03 second when the serum calcium level became normal. Three patients showed no changes and one showed a slight prolongation of the P-R interval after surgery. Five patients with marked hypercalcemia had absolute prolongation of the P-R interval ranging from 0.20 to 0.24 second.

*QRS Interval:* The duration and configuration of the QRS interval was not affected by

TABLE II

The Intervals of the Ventricular Complex in Twenty-Three Patients with Marked Hypercalcemia from Etiologies Other than Hyperparathyroidism

| Case No. | Diagnosis | Age (yr.) and Sex | Serum Calcium (mg./100 ml.) | Intervals (hundredths of second) | | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | R-R′ | P-R | Q-oTc | Q-aTc | Tc | Q-Tc | |
| 1 | Carcinoma of esophagus | 70,M | 24.0 | 80 | 20 | 16 | 26 | 25 | 40 | Anemia, cardiomegaly |
| 2 | Multiple myeloma | 29,F | 22.4 | 55 | 14 | 20 | 30 | 20 | 40 | Anemia, cardiomegaly (Fig. 3) |
| 3 | Carcinoma of breast | 54,F | 22.1 | 52 | 18 | 20 | 33 | 28 | 47 | |
| 4 | Carcinoma of breast | 39,F | 20.2 | 54 | 16 | 18 | 27 | 15 | 33 | Anemia (Fig. 2) |
| 5 | Carcinoma of esophagus | 70,M | 18.5 | 92 | 24 | 13 | 21 | 22 | 34 | |
| 6 | Carcinomatosis* | 70,M | 18.5 | 76 | 16 | 18 | 30 | 20 | 38 | Ventricular extrasystoles |
| 7 | Breast carcinoma | 57,M | 17.7 | 62 | 16 | 22 | 24 | 19 | 40 | Left bundle branch block |
| 8 | Alveolar cell carcinoma of lung | 69,M | 17.7 | 46 | 12 | 16 | 32 | 22 | 38 | |
| 9 | Carcinoma of breast | 47,F | 17.4 | 46 | 10 | 21 | 34 | 25 | 46 | |
| 10 | Carcinoma of pharynx | 45,M | 17.3 | 66 | 18 | 17 | 28 | 22 | 39 | Anemia |
| 11 | Hodgkin's disease | 19,M | 17.2 | 58 | 14 | 18 | 29 | 17 | 35 | Anemia (Fig. 2) |
| 12 | Carcinomatosis* | 52,F | 17.2 | 64 | 15 | 18 | 28 | 18 | 35 | |
| 13 | Multiple myeloma | 64,F | 17.2 | 63 | 16 | 21 | 29 | 20 | 42 | Mild congestive heart failure |
| 14 | Carcinomatosis* | 70,F | 17.1 | 52 | 20 | 22 | 33 | 17 | 39 | Cardiomegaly, digitalized (Fig. 3) |
| 15 | Carcinoma of pharynx | 60,M | 17.0 | 51 | 12 | 23 | 35 | 29 | 46 | Cardiomegaly |
| 16 | Carcinoma of bladder | 64,F | 16.8 | 58 | 16 | 16 | 30 | 18 | 34 | |
| 17 | Reticulum cell sarcoma | 68,F | 16.0 | 56 | 16 | 21 | 29 | 20 | 45 | Anemia |
| 18 | Carcinomatosis* | 64,M | 15.9 | 55 | 16 | 22 | 38 | 23 | 45 | |
| 19 | Carcinoma of breast | 60,F | 15.7 | 62 | 13 | 18 | 31 | 21 | 39 | |
| 20 | Carcinoma of esophagus | 80,M | 15.7 | 72 | 16 | 23 | 35 | 18 | 41 | |
| 21 | Multiple myeloma | 59,M | 15.7 | 60 | 20 | 15 | 28 | 23 | 38 | Anemia |
| 22 | Carcinomatosis* | 51,M | 15.6 | 70 | 20 | 17 | 29 | 22 | 38 | |
| 23 | Multiple myeloma | 64,M | 15.5 | 80 | 16 | 13 | 28 | 26 | 39 | Anemia |

* Primary lesion unknown.

hypercalcemia. Right bundle branch block and left bundle branch block were observed one time each in both groups of patients. The amplitude of the R and S waves was unchanged in the hyperparathyroid patients after surgery.

*The Q-Tc Interval:* In hyperparathyroidism a decrease in the duration of the Q-Tc interval was observed in eight of twelve patients. The average Q-Tc was 0.37 second and the range was 0.34 to 0.41 second (Table III). Following surgery in nine patients and restoration of a normal serum calcium level, the duration of the Q-Tc interval increased in all but one. The average duration after surgery was 0.42 second and the range was 0.36 to 0.53 second. These values are normal for women.[7] In the patients with marked hypercalcemia from other causes the average Q-Tc of 0.40 second was slightly longer than for patients with hyperparathyroidism (Table III). The lengthening was due to an increase in the duration of the T wave often noted in this group.

*The Q-oTc segment.* In hyperparathyroidism the mean Q-oTc was 0.19 second and the range was 0.15 to 0.25 second prior to surgery. After surgery, when a normal serum calcium level had been restored, the mean Q-oTc was 0.23 second and the range was 0.19 to 0.33 second (Table III). The mean Q-oTc and range in the patients with marked hypercalcemia were virtually identical to those observed in untreated patients with hyperparathyroidism prior to surgery although the mean serum calcium level was much greater.

*The Q-aTc segment.* The changes observed were of the same order as those described for

TABLE III

Summary of the Changes in the Intervals of the Ventricular Complex in Hyperparathyroidism and in Marked Hypercalcemia from Other Etiologies

| Group | Number of Patients | Serum Calcium (mg./100 ml.) | Intervals (hundredths of second) | | | | P-R Prolonged |
|---|---|---|---|---|---|---|---|
| | | | Q-oTc | Q-aTc | Tc | Q-Tc | |
| Hyperparathyroidism Normocalcemia (after surgery) | 9 | 10.1* (9.4–10.9) | 23 (19–33) | 33 (28–44) | 18 (15–23) | 42 (36–53) | 0 |
| Hypercalcemia (before surgery) | 11† | 13.8 (12.4–16.0) | 19 (15–25) | 29 (26–35) | 18 (13–22) | 37 (34–41) | 2‡ |
| Marked hypercalcemia from other etiologies | 23 | 17.8 (15.5–24.0) | 19 (13–23) | 30 (21–38) | 21 (15–29) | 40 (33–47) | 5 |

* Mean range in parentheses.
† Case 12 with azotemia excluded.
‡ Five additional patients showed shortening of the P-R interval after surgery (see text).

the Q-oTc segment. The apex of the T wave showed no tendency to shift its position with a change in the serum calcium from high to normal levels.

*The Tc segment.* In hyperparathyroidism the average duration of the T wave was 0.18 second both before and after surgery. The range differed slightly (Table III). In the patients with marked hypercalcemia the average duration of the T wave was 0.21 second and the range, 0.15 to 0.29 second.

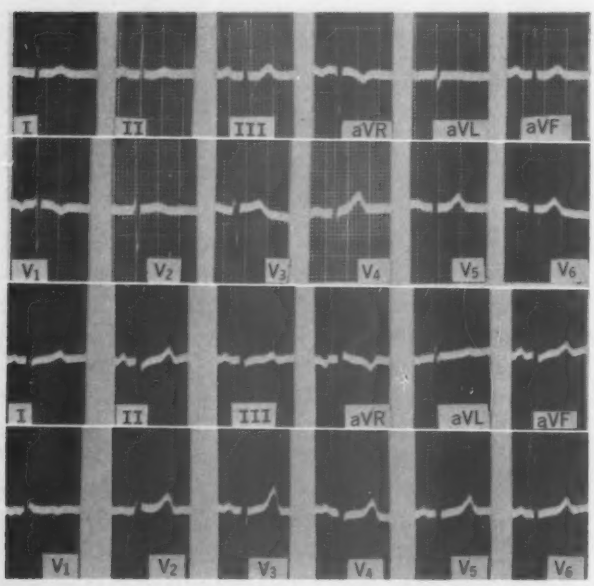



FIG. 1. (Case 2, Table I.) Hyperparathyroidism in a thirty-four year old woman. *Above*, preoperative electrocardiogram; serum calcium is 15 mg. per 100 ml. *Below*, postoperative electrocardiogram, during transient tetany; serum calcium is 8 mg. per 100 ml. Note shortening of P-R interval and prolongation of Q-oTc segment as serum calcium decreases. These represent the greatest change observed before and after surgery in the patient with hyperparathyroidism.

In hyperparathyroidism the configuration of the T waves appeared normal prior to surgery. The electrocardiograms of two patients, however, showed the T wave changes of left ventricular hypertrophy. Following surgery and restoration of a normal serum calcium level no significant changes in T wave contour were observed. In one patient, however, inversions of the T waves appeared (Case 2) when transient hypocalcemic tetany developed after surgery. The electrocardiograms of another patient with transient postoperative tetany showing the maximum changes observed before and after surgery for hyperparathyroidism are illustrated in Figure 1. In the patients with marked hypercalcemia, inversions of the T waves were observed four times and flattening twice. These aberrations could not be attributed to hypercalcemia alone for each of these patients had either cardiomegaly or anemia. When the Q-oTc segment was virtually absent the leads from the right side of the precordium often showed a characteristic appearance as the take-off of the ascending limb of the S wave merged without interruption into the ascending limb of the T wave (Fig. 2). When the T waves were inverted, the virtual absence of the Q-oTc segment gave a "scooped" appearance (Fig. 3)

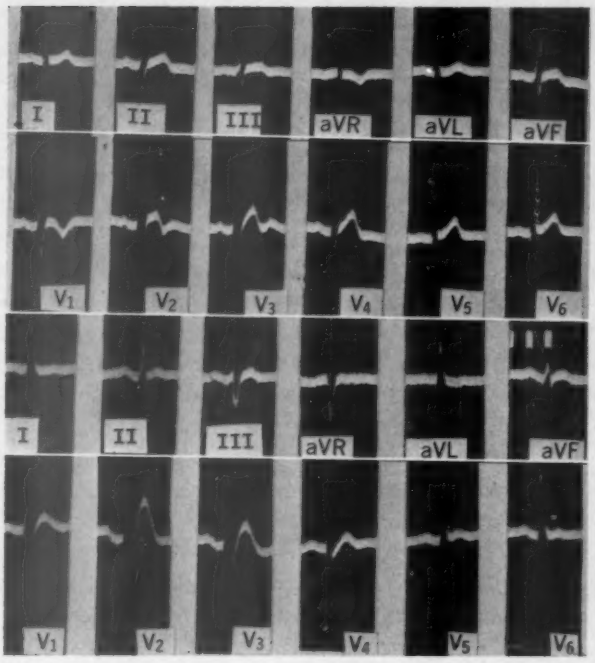



FIG. 2. *Above*, Hodgkin's disease in a nineteen year old man (Case 11, Table II). Serum calcium is 17.2 mg. per 100 ml. Note virtual absence of Q-oT segment and prominent U wave in leads $V_2$ and $V_3$. *Below*, carcinoma of the breast in a thirty-nine year old woman (Case 4, Table II). Serum calcium is 20.2 mg. per 100 ml. Note virtual absence of Q-oT segment. In leads $V_2$ and $V_3$ the ascending limb of the S wave merges directly into the ascending limb of the T wave.

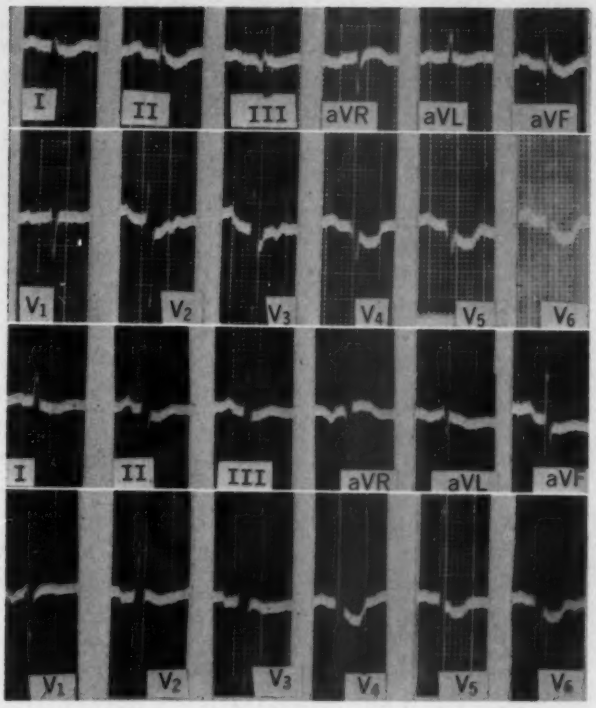



FIG. 3. *Above*, carcinomatosis in a seventy year old woman (Case 14, Table II) with cardiomegaly receiving digitalis. Serum calcium is 17.1 mg. per 100 ml. Note "scooped" T waves in leads $V_4$-$V_6$ and U waves in $V_2$-$V_3$. *Below*, multiple myeloma in a twenty-nine year old woman with anemia and cardiomegaly (Case 2, Table II). Note "scooped" T waves.

which did not resemble the straight line or check mark configuration associated with digitalis. In both groups a rounding of the apex of the T waves was sometimes observed.

*The Q-U Interval:* U waves were observed in one patient with hyperparathyroidism and in six patients with marked hypercalcemia (Figs. 2 and 3) and were of normal appearance and amplitude. The duration of the Q-U interval was not affected by an elevation of the serum calcium level.

*Effect of Intravenous Calcium:* Two patients with hyperparathyroidism received intravenous infusions of 5 per cent calcium gluconate during a loading test (Howard[8]). Serum calcium levels rose in three hours from 11.9 to 13.7 mg. per 100 ml. in one and from 11.8 to 13.4 mg. per 100 ml. in the other. A bradycardia was produced in both patients. Other than this, the effect of a further rise in the serum calcium level upon the intervals of the electrocardiogram and contour of the complexes was minimal.

## COMMENTS

*Hypercalcemia due to Hyperparathyroidism:* The literature concerning the electrocardiogram in hyperparathyroidism is surprisingly scanty and consists of nine reports describing the graphs of ten patients.[1–5, 9–12] Ballin's[1] early report called attention to the presence of a short S-T segment prior to surgery which lengthened after resection of a parathyroid adenoma. Subsequent publications stressed the shortening of the Q-Tc interval but this was soon recognized to be a consequence of the decreased duration of the S-T segment.[11] Ballin suggested that a short S-T segment might prove a reliable clinical sign for the electrocardiographic diagnosis of hypercalcemia. In practice, the Q-Tc interval is unreliable as a guide to the presence of hypercalcemia and the S-T segment is difficult to measure accurately. However, when the S-T segment is virtually absent, the ascending limb of the S wave merges in one sharp upstroke with the ascending limb of the T wave and imparts a characteristic appearance to the electrocardiogram which may be of value in assessing the presence of hypercalcemia.[4] Additional electrocardiographic changes which have been described in hyperparathyroidism are prolonga-

tion of the P-R interval[3] and a broad rounding of the apex of the T wave.[4] Definite inversion of the T waves has been described in a patient with a functioning parathyroid carcinoma and "parathyroid poisoning" who at autopsy had scattered areas of necrosis throughout the myocardium.[5]

The present study extends and reaffirms earlier observations of the effect of hypercalcemia due to hyperparathyroidism on the electrocardiogram. Determination of the Q-oTc segment provides an indirect measurement of the S-T segment for the QRS interval, which is included, is not affected by changes in the levels of serum calcium. This procedure eliminates the uncertainties arising from difficulties inherent in precise determination of the RS-T junction. The duration of the Q-oTc segment has in our hands been as reliable a guide to hypercalcemia as it is to hypocalcemia.[6,13] The apparent shortening of the Q-Tc interval is proportional to the changes in the Q-oTc segment, for the duration of the T wave is not affected by the levels of serum calcium observed in this series of hyperparathyroidism. At levels of serum calcium above 16 mg. per 100 ml. prolongation of the Tc wave may occur. Thus, the patient of Bradlow and Segel[4] with hyperparathyroidism and a serum calcium level of 21 mg. per 100 ml. showed a Tc wave duration of 0.24 second. The present study also shows that in marked contrast to the effect of lowering the serum calcium observed in hypoparathyroidism[6] elevation of the serum calcium usually does not affect the polarity of the T wave. Lastly, elevation of the serum calcium level as observed in hyperparathyroidism does not affect the cardiac rhythm, the P wave and the Q-U interval of the electrocardiogram.

*Hypercalcemia from Other Causes:* The literature about the electrocardiogram in hypercalcemia from etiologies other than hyperparathyroidism is also scarce and is difficult to interpret because of the presence of associated organic disease which independently affects the myocardium.[10,14–16] Hypercalcemia induced by excessive intake of vitamin D is most likely to simulate the clinical condition of hyperparathyroidism and it is not surprising, therefore, that similar electrocardiographic findings have been described.[11] A much more serious situation arises when the serum calcium level is raised acutely in normal subjects by intravenous infusions. Then bradycardia, flattening and inversion of the T waves and also the P waves are frequent and ventricular extrasystoles, sinus arrhythmia, shifting of the pacemaker, various degrees of heart block and sinus arrest may occur.[17,18]

In the present study, the effects of marked hypercalcemia upon the electrocardiogram in patients without diseases of the parathyroid glands are similar to those observed in patients with hypercalcemia from hyperparathyroidism in spite of the greater mean level of serum calcium present. The previous observation that shortening of the Q-Tc interval is less helpful in the electrocardiographic assessment of hypercalcemia than it is in hypocalcemia is explained by the fact that at these levels prolongation of the T waves also may occur and annul the effect produced by shortening of the Q-oTc segment. The Q-oTc segment, therefore, is the best indication of hypercalcemia as judged from the electrocardiogram.[3] Although one of the patients in this series was receiving digitalis without untoward effect, there seems little doubt that its administration under these circumstances is hazardous and should be avoided.[19]

## Summary

The electrocardiograms of twelve patients with hyperparathyroidism and twenty-three patients with marked hypercalcemia from various other etiologies have been studied. In nine patients with hyperparathyroidism repeat electrocardiograms were available for comparison following restoration of the normal serum calcium level. In all patients shortening of the Q-oTc duration was inversely proportional to the serum calcium level. The Q-Tc interval was inversely proportional to the serum calcium level only up to levels of 16 mg. per 100 ml. At levels greater than this, prolongation of the T waves was observed and the Q-T duration, therefore, became disproportionately long. The Q-oTc duration was, however, an accurate electrocardiographic guide to levels of serum calcium up to 20 mg. per 100 ml. A tendency toward prolongation of the P-R interval was often observed. Severe elevation of the serum calcium apparently has no effect upon either the polarity of the T waves, the cardiac rhythm, the P wave, the QRS or the Q-U intervals.

## Addendum

Since the submission of this manuscript, Crum and Till[20] have reported the occurrence of the Wenckebach phenomenon in a patient with hyperparathyroidism whose serum calcium level was 15.3 mg. per 100 ml.

Following resection of a parathyroid adenoma and lowering of the serum calcium level to 8.9 mg. per 100 ml., a normal cardiac rhythm was restored. Since atropine abolished the arrhythmia prior to surgery, the authors attributed the phenomenon to excessive vagal action induced by hypercalcemia.

## References


1. Ballin, M. Parathyroidism. *Ann. Surg.*, 96: 649, 1932.
2. Kellogg, F. and Kerr, W. J. Electrocardiographic changes in hyperparathyroidism. *Am. Heart J.*, 12: 346, 1936.
3. Waife, S. O. Hyperparathyroidism and partial heart block. *J. Lab. & Clin. Med.*, 32: 185, 1947.
4. Bradlow, B. A. and Segel, N. Acute hyperparathyroidism with electrocardiographic changes. *Brit. Med. J.*, 2: 197, 1956.
5. Rapoport, A., Sepp, A. H. and Brown, W. H. Carcinoma of the parathyroid gland with pulmonary metastases and cardiac death. *Am. J. Med.*, 28: 443, 1960.
6. Bronsky, D., Dubin, A., Waldstein, S. S. and Kushner, D. S. Calcium and the electrocardiogram. I. The electrocardiographic manifestations of hypoparathyroidism. *Am. J. Cardiol.*, 7: 823 1961.
7. Bazett, H. C. An analysis of the time relations of the electrocardiogram. *Heart*, 7: 353, 1918.
8. Howard, J. E., Hopkins, T. R. and Connor, T. B. The use of intravenous calcium as a measure of activity of the parathyroid glands. *Tr. A. Am. Physicians*, 65: 351, 1952.
9. Korth, C. and Hecht, H. Das Elektrokardiogramm bei Osteitis Fibrosa Cystica Generalisata (Recklinghausen). *Klin. Wchnschr.*, 17: 21, 1938.
10. Schrumpf, A. and Harbitz, H. F. A case of hyperparathyroidism with nephrocalcinosis and azotemia. *Acta chir. Scandinav.*, 80: 199, 1938.
11. Ljung, O. Elektrokardiogrammet vid hyperkalcemi. *Nord. med.*, 42: 1364, 1949.
12. Beck, G. H. and Marriott, H. J. L. The electrocardiogram in hyperparathyroidism. *Am. J. Cardiol.*, 3: 411, 1959.
13. Bronsky, D., Dubin, A., Kushner, D. S. and Waldstein, S. S. Calcium and the electrocardiogram. III. The relationship of the intervals of the electrocardiogram to the level of serum calcium. *Am. J. Cardiol.*, 7: 840, 1961.
14. Goldberger, E. Unipolar Lead Electrocardiography and Vectorcardiography, p. 271. London, 1953. Kimpton.
15. Lepeschkin, E. Modern Electrocardiography. Vol. 1, p. 289. Baltimore, 1951. Williams & Wilkins.
16. Yu, P. N. G. The electrocardiographic changes associated with hypercalcemia and hypocalcemia. *Am. J. M. Sc.*, 224: 413, 1952.
17. Berliner, K. The effect of calcium injections on the human heart. *Am. J. M. Sc.*, 191: 117, 1936.
18. Clark, N. E. The action of calcium on the human electrocardiogram. *Am. Heart J.*, 22: 367, 1941.
19. Gold, H. and Edwards, D. J. The effects of ouabain on the heart in the presence of hypercalcemia. *Am. Heart J.*, 3: 45, 1927.
20. Crum, W. D. and Till, H. J. Hyperparathyroidism with Wenckebach's phenomenon. *Am. J. Cardiol.*, 6: 838, 1960.

# Calcium and the Electrocardiogram

## III. The Relationship of the Intervals of the Electrocardiogram to the Level of Serum Calcium*

DAVID BRONSKY, M.D., ALVIN DUBIN, M.S., DANIEL S. KUSHNER, M.D. *and* SHELDON S. WALDSTEIN, M.D.

Chicago, Illinois

IT IS THE PURPOSE of this paper to study the correlation of the time relations of the electrocardiographic events of the ventricular repolarization process and the level of serum calcium. The known electrocardiographic manifestations associated with variation in the level of the serum calcium will be briefly reviewed.

### SUBJECTS AND METHOD

One hundred fourteen electrocardiograms obtained from twenty-two patients with hypoparathyroidism, twelve patients with hyperparathyroidism and twenty-three patients with marked hypercalcemia of various other etiologies were studied. Included are serial electrocardiograms obtained as the serum calcium was restored to normal levels by appropriate therapy in all but the last group of patients. The serum calcium level was determined prior to the recording of each electrocardiogram. Additional clinical details, the method of recording and measuring the intervals of the electrocardiograms have been presented in two preceding papers.[1,2]

### RESULTS

*Q-oTc Segment:* The duration of the Q-oTc segment of the electrocardiogram was plotted against the serum calcium level as shown in Figure 1. A least squares linear regression line derived from the data was statistically significant. However, analysis of variance showed a large remaining source of deviation from linear regression. The data, therefore, were further analyzed by the technic of curvilinear regression as shown in Figure 2. The predictive quadratic equation obtained was

$$\hat{Y} = 48.3645 - 3.1693X + 0.0809X^2.$$

Analysis of variance revealed that the additional reduction in deviation from regression resulting from fitting the second order equation was highly significant ($p < 0.001$), with little residual deviation from curvilinear regression.

The curve obtained (Fig. 2) shows that the duration of the Q-oTc segment decreases as the serum calcium level rises. The degree by which it diminishes, however, becomes gradually less and reaches a minimum at a serum calcium level of 20 mg. per 100 ml. At still higher levels the curve turns slightly upward.

*Tc Waves:* A plot of the duration of the Tc wave against the serum calcium level is shown in Figure 3. Analysis showed no significant linear regression. The duration of the T wave was largely independent of the serum calcium level. However, absolute prolongation of the Tc wave duration was observed in general at serum calcium levels above 16 mg. per 100 ml. In individual cases prolongation also was observed with hypocalcemia.[1]

*Q-Tc Interval:* The duration of the Q-Tc interval was plotted against the serum calcium level and is shown in Figure 1. Like the Q-oTc segment, this parameter secured its best fit when analyzed by curvilinear regression. The predictive quadratic equation obtained was

$$\hat{Y} = 74.4300 - 4.4240X + 0.1328X^2$$

which is highly significant ($p < 0.001$).

The curve obtained (Fig. 2) parallels the curve for the Q-oTc segment up to a serum calcium level of 16 mg. per 100 ml. The upward turn of the curve at higher levels is ap-

* From the Hektoen Institute for Medical Research and the Endocrine Clinic of the Cook County Hospital; and the Departments of Medicine of the University of Illinois College of Medicine and Northwestern University Medical School, Chicago, Illinois. These studies were supported in part by a grant from the Dr. Leonard H. and Louis D. Weissman Medical Research Foundation.

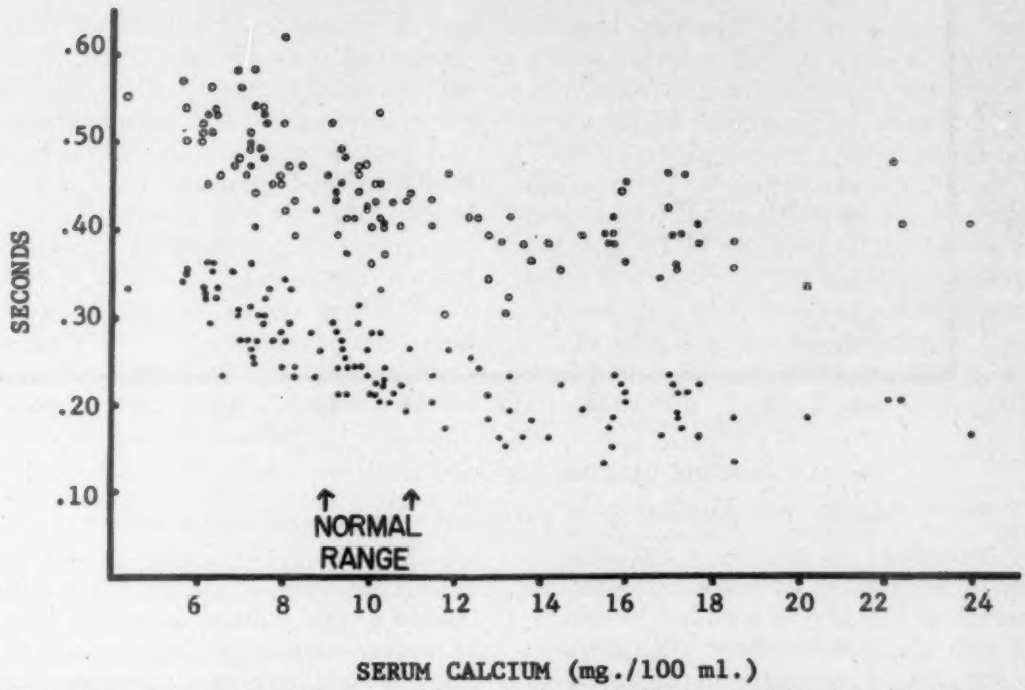



FIG. 1. The relation of the Q-Tc interval (open dots) and Q-oTc segment (closed dots) to the serum calcium level.

parently due to the prolongation of the Tc wave which generally occurs at these levels, for this segment is included in the measurement of the interval.

## COMMENTS

Previous statistical studies of the relationship of the duration of the Q-Tc interval and the S-T segment to the serum calcium level have yielded significant straight line regression equations.[3–5] None of these studies, however, included patients with serum calcium levels greater than 16 mg. per 100 ml. The inclusion in this study of patients with marked hypercalcemia demonstrates that this relationship is best expressed as a curve, the interpretation of which provides a better explanation of the observed events.

The primary and principal effect of the serum calcium level is upon the duration of the S-T segment of the ventricular repolarization process as observed electrocardiographically.[3] At extraordinarily high levels prolongation of the T wave segment also occurs. The depolarization process, represented by the duration of the QRS interval, is not affected; therefore, a spurious prolongation of the Q-Tc interval is produced at very high serum calcium levels. This explains the frequent observation that the Q-Tc interval, although an excellent guide to hypocalcemia, is often an inaccurate guide to hypercalcemia as judged from the electrocardiogram.

The Q-oTc segment provides an indirect measurement of the S-T segment which obviates the difficulties inherent in precise location of the RS-T junction and thereby eliminates uncertain-

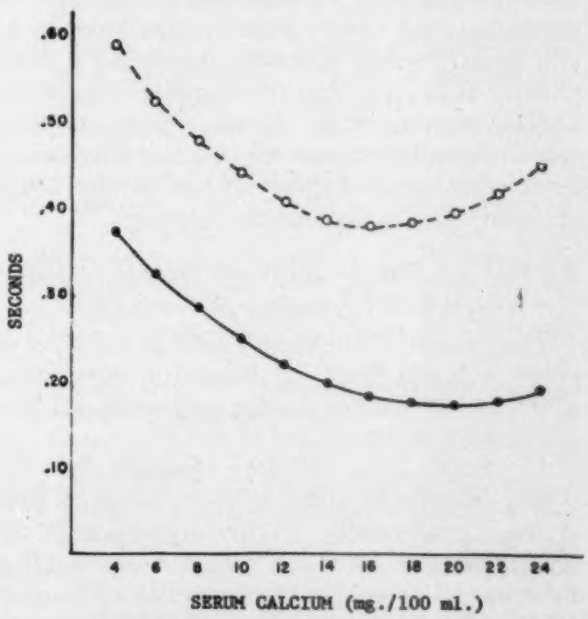



FIG. 2. Predicted duration of Q-Tc interval (-o-o-) and Q-oTc segment (----) for given serum calcium level based on curvilinear regression analysis of data from Figure 1. See text for predictive equations.

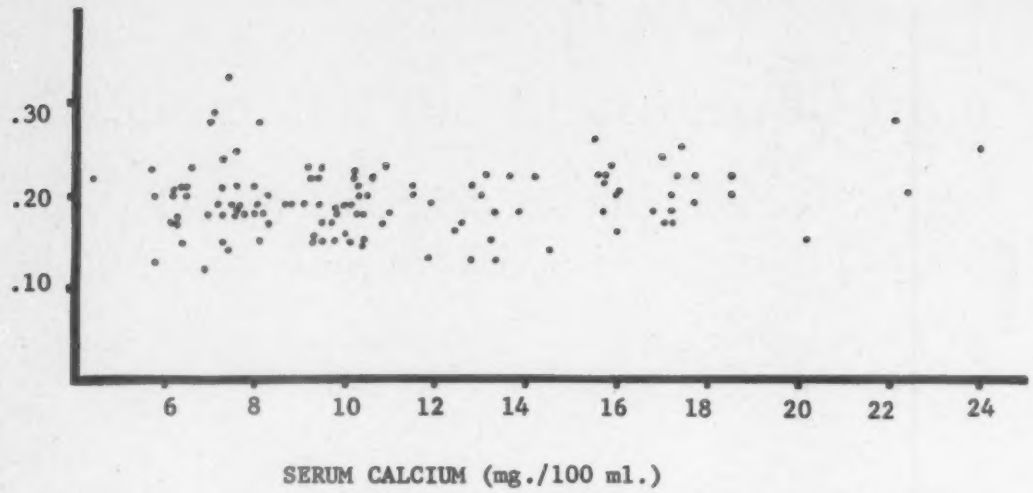



FIG. 3. The relation of the Tc wave duration to the serum calcium level.

ties in its measurement. The shortest possible measurement of the Q-oTc segment would be identical with the duration of the QRS interval which is not affected by the serum calcium level and generally has a range in this study of 0.06 to 0.10 second. In practice, very few individual patients approach this limit. The limiting value obtained by curvilinear regression was 0.17 second and occurred at a serum calcium level of 20 mg. per 100 ml. This, perhaps, represents an average physiologic limit beyond which further shortening of the S-T segment cannot occur. Such a level of serum calcium is incompatible with long life and the increase in duration of the Q-oTc segment which occurs at still greater levels probably represents a toxic effect. It is clear that the measurement of the Q-oTc segment is the superior guide to electrocardiographic assessment of the serum calcium level when other factors known to affect this segment, such as digitalis, are excluded.

## REVIEW OF THE EFFECTS OF SERUM CALCIUM UPON THE ELECTROCARDIOGRAM

The known effects of variation in the level of serum calcium upon the human electrocardiogram, as determined in this and other studies, are as follows[1-10]:

*1. Heart Rate:* Acute elevation of the serum calcium level by calcium infusions produces a bradycardia. Acute depression of the serum calcium level by infusions of chelating substances causes a tachycardia. In most clinical situations, however, the cardiac rate cannot be correlated with changes in the serum calcium level.

*2. Rhythm:* Normal sinus rhythm is present at all levels of serum calcium in the undigitalized human subject without coexisting heart disease. However, rapid, unphysiologic infusions of calcium solutions may produce arrhythmias and even cardiac arrest.[6] Other effects will be mentioned in the comment on digitalis.

*3. P-R Interval:* The duration of the P-R interval is increased at levels of serum calcium above normal limits. The converse, i.e., shortening of the interval at low levels, is not observed. The configuration of the P wave is not affected by changes in the serum calcium level.

*4. QRS Interval:* No variations in the duration and contour of the QRS interval are observed in relation to the serum calcium level in normal persons without coexisting heart disease.

*5. Q-oTc Segment:* The principal effect of the serum calcium level upon the electrocardiograms is on the S-T segment for which the Q-oTc segment provides a more nearly accurate, although indirect, measurement. The duration of the Q-oTc segment is inversely proportional to the level of serum calcium at all physiologic levels. The amount by which the duration of the Q-oTc segment decreases as the serum calcium level rises becomes progressively smaller. The duration of the Q-oTc segment rapidly diminishes toward normal limits when infusions of intravenous calcium are given to patients with hypocalcemia.

*6. T Wave:* The duration of the Tc wave is not affected by physiologic levels of serum calcium. At very high levels of serum calcium and in certain individual patients with hypocalcemia prolongation of the T wave may occur. The contour of the T wave is affected by both hypo-

calcemia and hypercalcemia. In the former instance the apex of the T wave is peaked; in the latter it is broad and rounded. The effect of hypocalcemia upon the polarity of the T wave is striking. Sharp, symmetrical, late inversion of the T wave is the abnormality most commonly observed, but tall, tented T waves also are observed. In approximately half of the patients the T waves appear within normal limits. When abnormalities of the T wave polarity occur they are not corrected by acute elevations of the serum calcium level by infusions but are corrected when the normal serum calcium level is restored gradually by specific therapy. Elevation of the serum calcium level has no effect upon the polarity of the T wave in patients without coexisting heart disease.

*7. Q-Tc Interval:* The duration of the Q-Tc interval is inversely proportional to serum calcium levels up to 16 mg. per 100 ml. At levels greater than this, prolongation of the interval is observed because of prolongation of the T wave included in the measurement of this interval. This interval, therefore, is of limited usefulness in assessing the presence of hypercalcemia from the electrocardiogram.

*8. Q-U Interval:* The duration of the Q-U interval and the contour and polarity of the U wave are not affected by variations in the level of serum calcium. The U wave is obscured in hypocalcemia by the descending limb of the T wave as the Q-T interval becomes prolonged.

*9. Digitalis:* In the digitalized person infusions of calcium potentiate the effect of digitalis, cause arrhythmias and are hazardous. When used with caution and judgment such infusions may indicate the degree of prior digitalization.[7,8] Acute depression of the serum calcium level by chelating substances counteracts the effects of digitalis and may be of value in the treatment of arrhythmias due to digitalis intoxication.[9,10]

## Summary

The time relations of the electrocardiographic events of the ventricular repolarization process have been correlated with the level of serum calcium in a study of 114 electrocardiograms obtained from thirty-four patients with disease of the parathyroid gland and twenty-three other patients with marked hypercalcemia. The duration of the Q-oTc segment is inversely proportional to levels of serum calcium as high as 20 mg. per 100 ml. The duration of the Q-Tc interval is inversely proportional to the serum calcium level as high as levels of approximately 16 mg. per 100 ml. At higher levels its duration again grows longer. The duration of the T wave is independent of the serum calcium level but is often prolonged at very high levels and may also be prolonged at low levels in individual patients. The duration of the Q-oTc interval is the best guide to the assessment of the serum calcium level from the electrocardiogram.

The effects of the serum calcium level upon the human electrocardiogram have been briefly reviewed.

## Acknowledgment

We are grateful to Dr. Herbert C. Batson, PH.D., for advice and assistance in statistical methods. We are indebted to Miss Anne Costos and Mrs. Jane C. Edmunds for preparation of illustrations.

## References

1. Bronsky, D., Dubin, A., Waldstein, S. S. and Kushner, D. S. Calcium and the electrocardiogram. I. The electrocardiographic manifestations of hypoparathyroidism. *Am. J. Cardiol.*, 7: 823, 1961.
2. Bronsky, D., Dubin, A., Waldstein, S. S. and Kushner, D. S. Calcium and the electrocardiogram. II. The electrocardiographic manifestations of hyperparathyroidism and of marked hypercalcemia from various other etiologies. *Am. J. Cardiol.*, 7: 833, 1961.
3. Yu, P. N. G. The electrocardiographic changes associated with hypercalcemia and hypocalcemia. *Am. J. M. Sc.*, 224: 413, 1952.
4. Reynolds, T. B., Martin, H. E. and Homann, R. E. Serum electrolytes and the electrocardiogram. *Am. Heart J.*, 42: 671, 1951.
5. Jesserer, H. and Tölk, R. Das Elektrokardiogramm bei der Tetanie erwachsener. *Ztschr. Kreislaufforsch.*, 42: 13, 1953.
6. Berliner, K. The effect of calcium injections on the human heart. *Am. J. M. Sc.*, 191: 117, 1936.
7. Nalbandian, R. M., Gordon, S., Campbell, R. and Kaufman, J. A new, quantitative digitalis tolerance test based upon the synergism of calcium and digitalis. *Am. J. M. Sc.*, 233: 503, 1957.
8. Nalbandian, R. M., Gordon, S. and Kaufman, J. Calcium–digitalis tolerance test. A clinical report of the first 24 trials. *Am. J. M. Sc.*, 234: 391, 1957.
9. Jick, S. and Karsh, R. The effect of calcium chelation on cardiac arrhythmias and conduction disturbances. *Am. J. Cardiol.*, 4: 287, 1959.
10. Seven, M. J. The influence of calcium and trace metals on myocardial function. In: Edema: Mechanisms and Management, a Hahnemann Symposium on Salt and Water Retention, p. 684. Edited by Moyer, J. H. and Fuchs, M. Philadelphia, 1960. W. B. Saunders.

# Historical Milestones

## Coarctation of the Aorta (Meckel, 1750; Paris, 1791)

SAUL JARCHO, M.D.
New York, New York

WITH the present article we commence a series of studies of coarctation of the aorta, to be intercalated with the other articles in our historical series. From the viewpoint of the medical historian the study of a limited subject such as coarctation has distinct merits, since it brings into sharp focus the slow processes by which scientific knowledge develops.

We start with two of the earliest contributions on record. The first was presented by the famous Prussian anatomist Johann Friedrich Meckel (1714–1774) before the Royal Academy of Sciences of Berlin in 1750 and was printed in the sixth volume of the Memoirs of that Academy, collected and published at Avignon in 1768. The lapse of eighteen years between date of presentation and date of publication explains the fact that this basic case report has been cited in the literature under both dates.

* * *

### EXCERPTS FROM MECKEL'S PAPER ON COARCTATION

*Anatomical and physiological observation, concerning extraordinary dilatation of the heart, which came from the fact that the aortic conduit was too narrow.**

In his beautiful and useful book on the movement of the heart and on aneurysms, the famous Lancisi, a very accurate writer, undertook to present all the causes of aneurysm and dilatation of the heart which might be called *contra naturam*. He omitted one cause, which perhaps neither he nor any other author had ever seen and which nevertheless is able, almost alone, to cause enlargement of the whole heart. This cause is the aorta, when it is unnaturally narrow. Indeed, in the whole human body there is no proportional relation so necessary for health as that between the forces of the heart and those of the arteries. As soon as this comes to be altered the blood cannot move throughout the body with its usual freedom. If the strength of the heart is too great and the resistance of the vessels is too small, the blood by its mass overpowers the arteries and veins, dilates them, weakens them, and produces in them the bulges which are called aneurysms. Various remarkable cases of this have been reported by the author whom I have mentioned.[1] Additional cases are found in other books on the same subject. On the other hand, if the strength of the arteries exceeds that of the heart, the superfluity of blood produces a similar effect on the heart, which it relaxes and dilates far beyond its natural state. This does not fail to cause more or less of a disturbance in the circulation. Cases of this kind occur fairly often in the literature and will be found in the works of Lancisi[2] and Kerckring.[3] One of the most unusual is given by Wepfer, who reported dilatation of the heart caused by ossification of the aorta and its valves. Nowhere is it reported that excessive narrowness of the aorta has caused similar dilatation followed by death. It is this which makes me consider it useful and even necessary to impart to the public a case report so rare as that which forms the subject of this memoir.

* The French text bears the subtitle "Traduit du Latin" (Translated from the Latin). I have not found the Latin original. The volume used for these excerpts is in the National Library of Medicine, to which grateful acknowledgment is made. (S.J.)

[1] De aneurismat., lib. I, propos. 38, and lib. II.
[2] De repentinis mort., lib. 2, obs. 2.
[3] Spicileg. observat. anat.

Some time ago, among the large number of cadavers with which our anatomical theater is so plentifully supplied, through the orders of the King and the work of the Directors, we had the body of an eighteen year old girl. The cadaver was quite slender. The chest was narrow, compressed and long. The limbs and bones were small and delicate. Since childhood the patient had been very choleric. She had led a sedentary life and had been almost continually occupied in sewing. From time to time she had been tormented by palpitation of the heart and by oppressions, which were followed by general trembling of the limbs. As she was of low class, the only treatment given consisted of spirits of wine, but the frequent use of this drink soon made her condition much worse. She was then reaching her fifteenth year, an age when menstruation would begin to appear. But since this failed to happen, her symptoms now became much more intense. Her body was in a state of continual agitation. Her pulse was always fluttery and the oppression and palpitation tortured her without respite. She became sadder day by day, and since she had no other resource than the liquor which I have mentioned, she was reduced to an incredibly miserable condition. A surgeon whom the parents called to treat her undertook to relieve the lack of menstruation by several phlebotomies and by appropriate medications, to which he added purges, but his work was in vain. After each bleeding and each dose of an irritant drug her condition would go from bad to worse. Finally, at the age of eighteen years, the menses having constantly refused to appear, the tremors of the body and pulse kept increasing and the palpitations having developed into veritable syncopes, the patient, devoid of strength and unable to sustain herself, took to bed. After four weeks in bed during which she had continual palpitation and extreme respiratory difficulty she died in a state of suffocation.

I dissected the cadaver myself. While injecting the arteries I found that all the branches of the aorta, and this vessel itself during its descent through the abdomen, were astonishingly narrow. When I opened the thorax the relative size of the aorta was even smaller, since the heart, which I had been intending to fill with an injection of wax, and which I therefore examined very carefully, occupied almost the whole left half of the small chest. The lungs were not adherent, either to the mediastinum or the pleura. I was astonished at the great size of the heart, which was enveloped loosely by the pericardium. I found the muscular substance of the ventricles softer and more relaxed than it should be. The left ventricle was perhaps no stronger than the right. All the veins and the chambers of the heart were distended with black blood. The pulmonary artery (Fig. 1, F) was very large in proportion to the aorta and was filled with thick and polypus* blood. The pulmonary sinus (Fig. 2, C) was ample and well filled and rose beyond the sinus of the vena cava (Fig. 1, D). As for the aorta (Fig. 1, G), it was so narrow that its diameter was smaller by half than that of the pulmonary artery, which it should have exceeded or at least equalled in calibre.[4] The entire heart was extraordinarily dilated and its apex had an obtuse contour because of the ventricles, which were expanded up to that point. Having filled it with the injection mass, so that the extended walls should display the more clearly to what extent the proportions had been altered, I had a picture made. In the two accompanying illustrations the anterior and posterior parts are represented, along with another heart also filled with injection mass. In the latter specimen the ventricles and vessels are of normal size. In this way the reader can perceive exactly how much the first heart was enlarged and how narrow the aorta was.

Observations made on cadavers have shown that the natural proportion of the great vessels of the heart is such that in an adult the diameter of the aorta is 13 lines of a Paris foot [about 27 mm.], the square of this is 169. If in the same heart the pulmonary artery has a diameter of 12 or $12^1/_2$, the squares of which are respectively 144 and 156, the proportion of the latter to the squares of the pulmonary veins is as 156 or 144 to 96, that is as 2 to 3.† The proportion of the sinus of the pulmonary vein and the sinus of the vena cava is much harder to determine. It has been given as 4 to 5. As for me, by judging hearts filled with waxen injection mass I have observed that the proportion is usually 7 to 6.

Now the vessels of our dilated heart have entirely different proportions. The diameter of the aorta (Fig. 1, G) where it issues from the

* *Polypus* is an old term for clot. (S. J.)

[4] My illustrious teacher M. de Haller has thus determined the proportion of the aorta and pulmonary artery. See his commentary on Boerhaave, vol. 2, p. 28, note (d) and p. 139, note (a) sub finem.

† A modern writer would state this as 3 to 2. (S. J.)

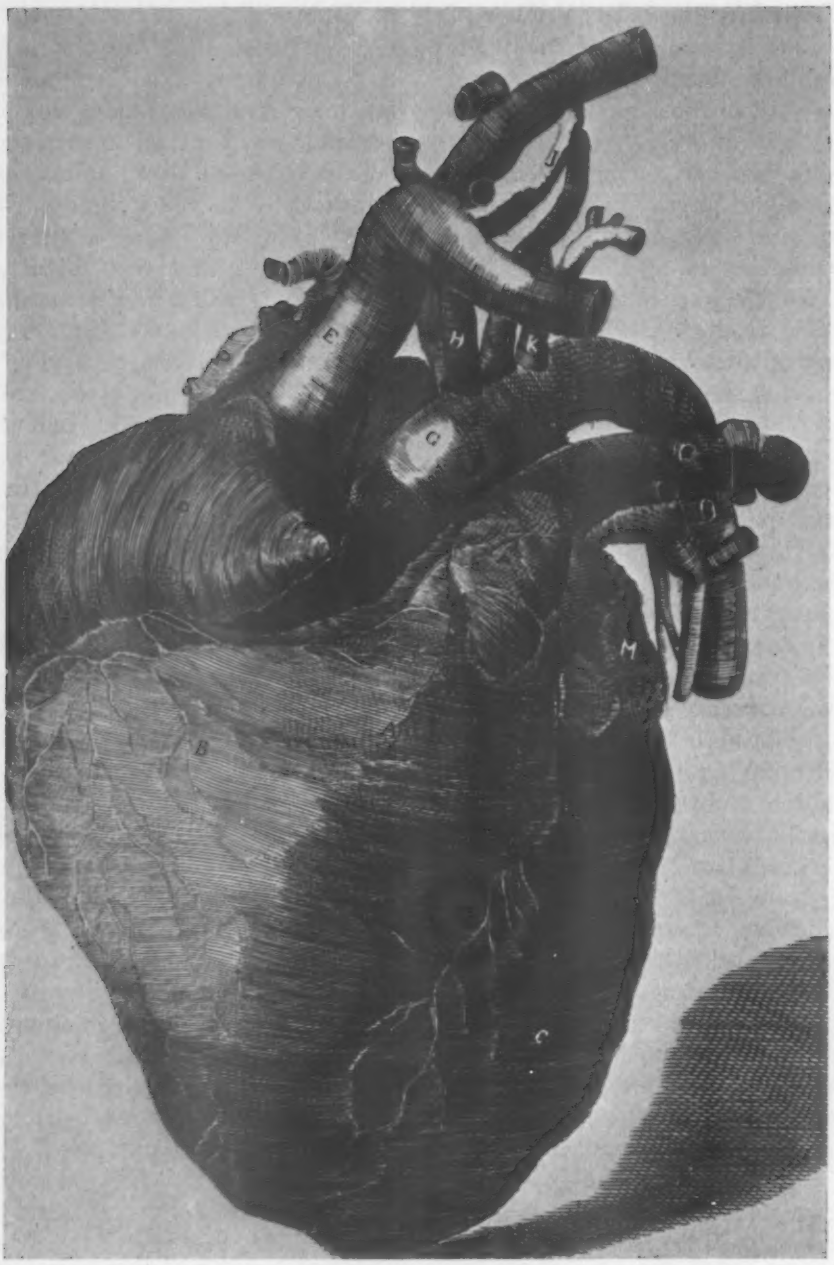


FIG. 1. Anterior surface of the dilated heart. A, anterior convexity of the heart. B, surface of right ventricle. C, anterior part of the left ventricle, which should be visible. D, right auricle. E, superior vena cava. F, pulmonary artery at exit from right ventricle. G, excessively narrow aorta. H, right subclavian artery. J, right carotid branch. K, left subclavian artery. L, left carotid branch. M, left auricle. N, pulmonary sinus, which passes between the vessels at the back of the heart. O, right superior pulmonary vein. P, branch of the right inferior pulmonary vein.

heart is 8 lines and that of the pulmonary artery (Fig. 1, E) is 13 lines. The squares are as 64:169. The squares of the diameters of all the pulmonary veins (Fig. 2, E, F, G, H, I) were to that of the pulmonary artery as 152 to 169. Thus the squares of the diameters of the pulmonary artery or of the five pulmonary veins taken together were to that of the aorta as $2^1/_2$ to 1. From this it follows that the pulmonary artery and veins carried one and a half times more blood than the aorta received from the left ventricle. This is a sufficient explanation of all the troubles which the poor patient suffered during her life.

Whenever the ancient physicians, in dissecting cadavers, found hearts that were larger than is usual, they inferred that the persons to whom these hearts belonged had been subject to choler. In

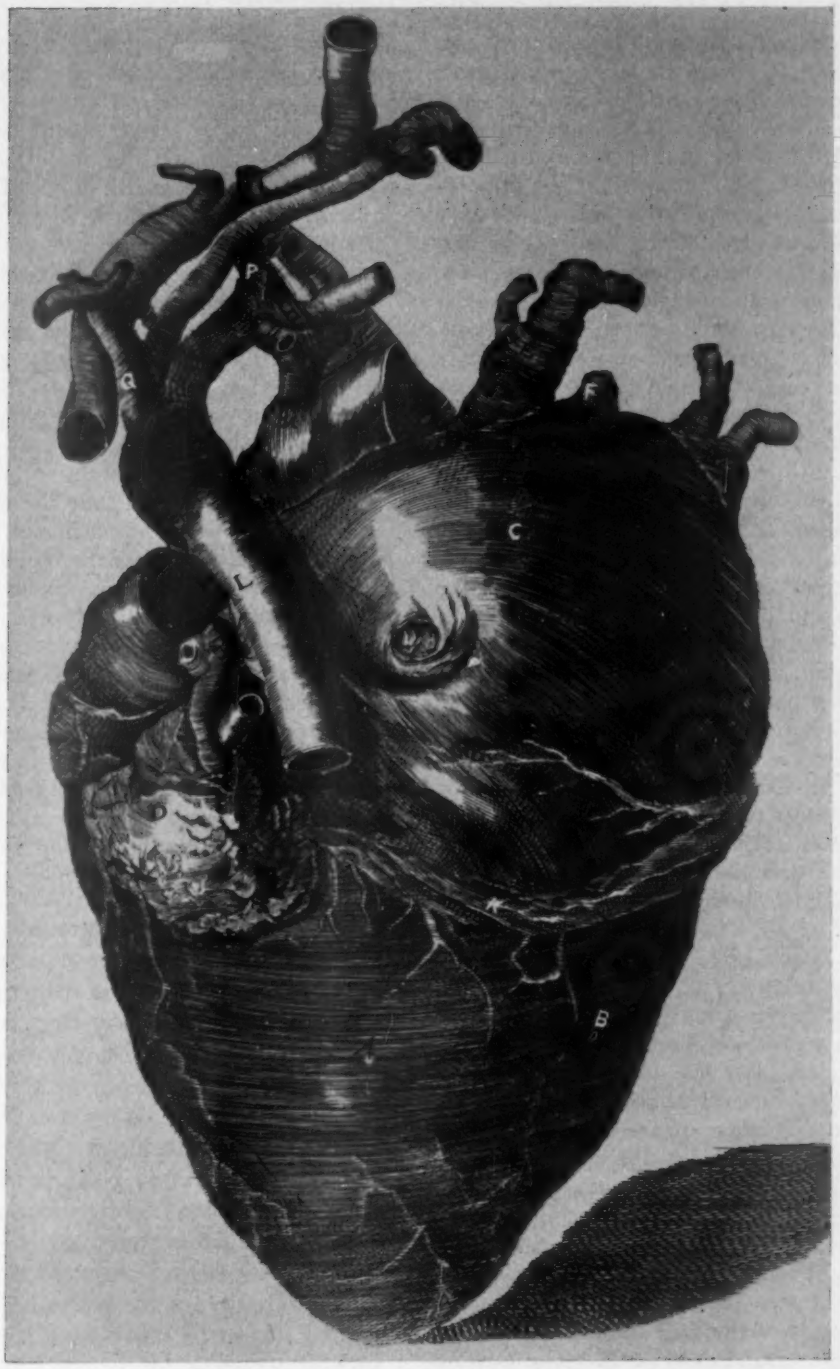



FIG. 2. Posterior surface of the same heart. A, convex surface of posterior or left ventricle. B, posterior part of right ventricle. C, ample pulmonary sinus (left atrium), greatly elevated above the right sinus. D, left auricle, attached to the right border of the sinus. E, very large right superior pulmonary vein. F, right pulmonary vein, very small. G, right inferior pulmonary vein. H, left superior pulmonary vein. K, trunk of the coronary vein. L, aorta, descending in an arch. M, right branch of the pulmonary artery. N, left branch of pulmonary artery, cut. O, right subclavian artery. P, right carotid artery. Q, left subclavian artery. R, left carotid artery. S, vena cava superior.

this they followed a commonly accepted opinion, without going carefully into the reason for the phenomenon. At the same time it is true that the size and softness of the heart, which are due to the resistance of the vessels, can dispose those who are in that condition to sadness and anger. When the arterial vessels are excessively resistant to the action which should empty the heart they receive too little blood and convey less to the brain and to other parts where the secretions are formed which the

body needs for its maintenance. In addition, this small amount of blood, which the heart propels with its remaining strength into the excessively contractile arterial vessels, is so rapidly urged forward that there is not enough time for the liquid to pass in the secretory channels nearby. Travelling too impetuously it throws itself into the veins and passes over the secretory channels. In addition the veins contain almost all the blood and are excessively swollen. Since the little orifices and the little channels of the secretory vessels are narrowed, both in the brain and elsewhere, there is a great obstacle to the regularity of secretion. The secretion of bile cannot occur more abundantly than the others, for although the hepatic blood terminates its course in the vessels of the portal vein and thus is subjected to lower pressure than the rest of the blood, yet the resistance which it experiences on leaving the liver through tributaries of the vena cava causes excessive dilatation in the branches of the portal vein. This compresses the secretory vessels and prevents the secretion of bile, in the same way that simple plethora causes a general obstacle to secretion. There remain in the blood the sharp and bilious components which should have been separated out and which give rise to various symptoms of jaundice and cerebral irritation. As long as blood is so abundant in all the veins of the body and in the lungs, the patient continually has a vexatious sensation caused by this repletion. He becomes incapable of activity and he falls into those attacks of sadness and choler which ordinarily occur in hypochondria.

Movement is annoying to persons in this condition, since the muscles are all swollen with venous blood and being at the same time deprived of the necessary quantity of nerve fluid, they can contract only with difficulty. But the more these patients avoid movement the more they become incapable of it and the more the cause of the disease—arterial resistance—increases. For it is absolutely necessary for the preservation of health that the blood should be driven in the veins by muscular movement. When movement is lacking the blood readily stagnates in the veins, which have no inherent contractile power. At least the circulation proceeds sluggishly because the arterial force is compelled unassisted to make the blood circulate through the veins. The muscles now come to lose their activity, the veins dilate more and more, the parts of the body spread, and the secretions continue to dwindle. Meanwhile the resistance of the arteries against the heart increases, because the heart excessively distended with blood, becomes to an equal degree incapable of overcoming the arterial resistance, being at the same time deprived of the necessary amount of nerve fluid. In our patient the diminished secretion of the latter substance, and of all the other substances, caused weakness of the body and trembling of the limbs.

In this case bleeding could produce no benefit. On the contrary, it necessarily made the illness worse. When the veins of a region are emptied of their blood, their resistance against the arteries diminishes. The less the arteries are resisted, the more the elastic force they acquire and exert upon the fluid that they contain, provided there remains a quantity of fluid sufficient for reacting. Their elastic force having increased, the arteries resist the heart more than before, when the resistance of the blood made them dilate more. The blood, being under greater pressure from the vessels, glides through them faster. Consequently the pressure of the arteries on the blood having increased its speed, the friction of its parts—and concomitantly the heat and rarefaction—become stronger. From this it appears that phlebotomy increases the resistance of the arteries against the heart and that the force of the heart can expel into them only a smaller quantity of blood. Meanwhile, the speed of the blood having increased, the veins receive the same amount of blood which they had received previously at a slower rate. This blood, more rarefied, distends the veins just as it did before the phlebotomy. This is why the veins of the entire body, including the heart and the lungs, supporting in the same proportion the load of a great quantity of blood, are in a state of tension. This arouses, instead of diminishing, all the symptoms of the disease—the oppression, tremor, palpitation, etc. The young woman under discussion had all these symptoms after phlebotomy.

When the heart receives one and a half times more blood than it can expel into the different parts of the body (as is shown by the fact that the squares of the diameters of the pulmonary artery and veins were one and a half times as large as that of the aorta) the heart can never empty itself well. By virtue of its naturally lax structure the anterior or right ventricle is much more distensible than the left or posterior ventricle. The complete evacuation of the latter cannot be prevented nor can its relaxation occur, except through extreme resistance of the aorta. This aortic resistance must produce symptoms much more violent than those which arise when it is merely the complete evacuation of the right ventricle that is impeded. For the blood continuously distending all the veins of the body and the pulmonary vessels as far as the heart, and being finally arrested at its emergence into the aorta, it incessantly loads the venous opening of the two ventricles. It enters the heart in a quantity one and a half times greater than that which is expelled into the body. The ventricles, which are never completely emptied, act incessantly on the blood remaining in them, since the blood newly entering irritates them and makes them con-

tract.[5] This continuous irritation of the heart and its excessively frequent action on the fluid which it contains, cause the fluttering of the pulse, the increased resistance producing the palpitation and finally the tremor and oppression which so greatly afflicted our patient and which arose only from the resistance of the aorta.

In this young woman the violence of all the symptoms increased rapidly whenever increased plethora caused new dilatation of the vessels of the whole body. In her sex the most inconvenient and dangerous years are those when the menses are ready to begin and those when they approach their end. At both periods the excess of blood in the vessels becomes the cause of many diseases. If the menses have not appeared at all, this is due to the fact that the blood is carried by the arteries to the natural parts in a quantity less than what is adequate for this excretion. Also, the excretory vessels of the uterus being too elastic, too narrow, and too strong, impede the blood with a resistance which the heart is in no condition to overpower. The region does not receive a quantity of blood sufficient to overcome the obstacles which oppose the appearance of the menses. In the absence of this evacuation the veins, excessively distended by the blood which they contain, would aggravate all the symptoms. From this time on, the respiratory difficulty must increase noticeably, because the excessively distended pulmonary vessels compress the bronchi. Likewise the tremor, the oppression and the palpitation must increase, because the quantity of blood which filled the cavities of the heart was greater than what they could cope with.

It should also be noticed that the remedies which the patient had employed and the kind of life she had led, were more likely to aggravate her condition than to alleviate it. I have observed above that phlebotomy increased the basic cause and the collateral causes of the disease, since it augmented the power of the arteries. But to this the surgeon had added emmenagogues. These, together with the purgatives, by their stimulant effect excited the vessels more and more to contract, whereas in order to obtain a salutary effect from drugs, the opposite result, namely vascular relaxation, should have been sought. At this time the patient herself increased the contractile tendency of the vessels by drinking spirits of wine. By this means she produced in the blood a degree of rarefaction which swelled the veins already overdistended by plethora alone, and caused compression in all regions. Inactivity and a sedentary life also retarded the return of blood through the veins and caused increasing stagnation. For this reason, when the patient remained in bed and all bodily movement ceased, the symptoms all increased rapidly, until the blood, distending the veins and all the cardiac chambers to an extreme degree, redoubled the palpitation and stopping in the pulmonary vessels—egress from the aorta being impeded—caused suffocation followed by death.

For this reason in the cadaver all the chambers of the heart, all the veins, and the pulmonary vessels, were filled with coagulated blood. This was necessarily the case because it was stagnation of this blood that caused death. As long as the heart could overcome the resistance of the aorta and could make the blood enter that vessel and its branches, there was no way in which the patient could die of suffocation. But the heart, being gradually weakened and relaxed, both by its extreme overfilling and by its excessive frequency of action, was finally unable to overcome the resistance of the aorta and relieve itself of its load of blood. Therefore its contraction ceased, its movement ceased, and death came. . .

Similar opinions* have been accepted by the majority of physiologists. Only the most modern have considered that resistance to the passage of the blood through the pulmonary artery might be responsible for dilatation of that artery and of the right ventricle. The smaller capacity of the veins has been attributed to condensation of the blood, causing it to occupy less space. Recently Aurivillius, a Swedish author, in a splendid dissertation on inequality of the cardiac chambers, has proved that the very circulation of the blood, by virtue of the various and frequent obstacles which it encounters in the lung, constitutes the reason why the right ventricle and the pulmonary artery are larger than the vein. He has shown that the pulmonary artery and the right ventricle are constructed in such a way as to yield readily to the amount of blood which causes dilatation, whereas the passage of blood across the pulmonary veins is not as free. Inspiration makes the blood go from the arteries into the pul-

[5] See the experiments which prove this in the inaugural thesis of M. Ens: *De causa vices alternas cordis producente*, Utrecht 1745, §37 et seq.

* Meckel here refers to opinions by Haller, Santorini, Senac, Helvetius and others on hemodynamics. The discussion has been omitted from the present translation. (S. J.)

monary veins, since it elongates the smallest venous branches which are closed and wrinkled in expiration; for this reason they resist filling at the time when they must receive the blood from the smallest branches of the pulmonary artery. Inspiratory dilatation of the lungs allows more space [for the venous branches] and lengthens them. From being compressed and oval in expiration they become more circular in inspiration; this greatly increases the channels. But expiration may last a little too long. This often happens during life, when we speak for a long time without taking a breath or when we do anything else that deprives the lungs of air. At such times a larger quantity of blood is drawn into the lung than can be removed in the same time through the pulmonary veins. In this way it happens that the smallest branches of these veins, partly obstructed by blood moving slowly in them, resist the current of blood brought by the pulmonary artery. From this it can be seen that it is absolutely necessary for the pulmonary artery and right ventricle to be more distensible than the pulmonary vein; otherwise blood arrested during passage from the smallest arterial ramifications into the corresponding veins might tear these thin branches if they were unable to yield. This gives an entirely satisfactory explanation of the phenomenon in question, namely, how it comes about that the dilatation of the right ventricle is greater than that of the left, and the dilatation of the pulmonary artery is greater than that of the vein. To this I see nothing to add. . .

I am far from agreeing with Helvetius and other physicians that refreshment and condensation of blood explain the narrowness of the pulmonary veins. These causes are insufficient to produce this condition of the veins and to maintain it when the free exit of blood from the left ventricle is arrested, as happened in our case, in which the proportion of these veins remained the same although the capacity of the pulmonary sinus (left atrium) was considerably increased.

Moreover, the great distensibility of the pulmonary sinus is a useful provision of nature, which protects the pulmonary veins from the pressure of the blood. Because of this structure it comes about that, just as the right ventricle can contain the blood which is arrested at its entry into the pulmonary artery and its passage through the lungs, in the same way the pulmonary sinus can hold the blood brought to it by the pulmonary veins, which has not been received into the left ventricle. This arrangement could readily be prejudicial to the body if the pulmonary veins were as distensible as those in the rest of the body. While distending they would obstruct the passage of blood arriving from the small branches of the pulmonary artery. In dilatation the veins, along with the arteries, would compress the pulmonary cells and block the entry of air. Accordingly Nature has decreed that the blood, having passed the narrow straits of the small arterial branches in the lung, can flow freely through the veins into the pulmonary sinus. For this reason she made five openings or small trunks, which end in a large distensible sac, to which the fluid is transported freely, without risk of regurgitation. . .

* * *

## Author's Comment on the Essays of Meckel and Paris

Meckel's essay is commonly stated to be the first description of aortic coarctation. The reader who has conscientiously read the excerpts which I have given in translation must decide for himself how much credit he wishes to give the distinguished anatomist for his scanty description.

The patient was an asthenic girl of eighteen years, who had suffered from palpitation, oppression, tremor, amenorrhea and dejection. She was poor and had almost no medical care: alcoholic liquor, purges, emmenagogues and phlebotomy constituted the whole treatment. Death occurred after symptoms of suffocation.

Meckel states that he performed the autopsy himself. Of the aorta he says merely that all its branches and the main trunk were marvellously narrow (*merveilleusement étroit*). The thoracic aorta seemed especially small because the heart was so large. He later adds that its diameter was smaller by one half than that of the pulmonary artery. This statement is supported by measurements and calculations of area. There is no description of the interior of the aorta or any other vessel and no mention of localized constriction or anastomoses. The analytic reader is left with the impression that the patient probably had diffuse aortic hypoplasia or perhaps elongated coarctation, and that she certainly had cardiac hypertrophy, although enlargement of individual chambers is not clearly described. Presumably there were evidences of congestion in the viscera, but these are not mentioned.

The greatest part of the text is devoted to discussions of hemodynamics. Much attention is paid to measurements of vascular diameters. Curiously the square of the diameter, rather than the square of the radius, forms the basis

of ratiocination. Much is said about arterial resistance. There is frequent reference to a hypothesis which resembles more recent concepts of backward failure.

Interestingly, Meckel attempted to explain the patient's psychic state as a consequence of circulatory disturbance which had allegedly impeded secretory activity. He noted also the possible effects of the patient's social condition on the state of her health.

While we must conclude that Meckel's description of the aorta is a disappointment, we must be sympathetic toward his struggle with physiologic problems.

To the verbose discursiveness of Meckel's essay, even more conspicuous in the unabridged original than in the half-length excerpt printed herein, the brief, concise paper by M. Paris offers an impressive contrast. This essay was published in Desault's *Journal de Chirurgie*, volume 2, pages 107 to 110, 1791. The full title, translated, is *Considerable Stenosis of the Thoracic Aorta, Observed at the Hôtel-Dieu of Paris, by M. Paris, Prosector of the Amphitheatre.* Paris noted the typical constriction near the ligamentum arteriosum, as well as slight prestenotic dilatation. He gave a rather detailed and accurate description of the anastomoses; apparently the first in the literature. Clinical facts are totally lacking in this presentation, and the case is regarded mainly as a curiosity of the dissecting room.

* * *

### The Case of M. Paris (1791)

Among the large number of cadavers which I injected for dissection during the winter of 1789, that of a very emaciated woman about 50 years old presented a peculiarity which was worth recording because of its rarity and because of the conclusions which might be drawn from it for the benefit of the art of medicine.

The injection by which the arteries were filled was made with equal parts of resin and tallow, and dyed with lampblack. Introduced into the beginning of the aorta, the material penetrated so easily that it would have been possible to inject much more than is ordinarily needed for the cadaver of an adult.

Since the body was very thin, before the dissection it was possible to see distinctly, on the sides of the chest, the trunks and branches of the thoracic arteries, which were much thicker and more tortuous than the normal. This led me to do the dissection with special care. Here is the result of my investigations and observations.

The part of the aorta which is beyond the arch, between the ligamentum arteriosum and the first inferior intercostal, was so greatly narrowed that it had at most the thickness of a goosequill. Hence in taking apart its walls, which had not decreased in this place, there remained only a very small lumen. The part of the vessel which was above the constriction was slightly dilated; the distal part was of normal caliber. The most careful dissection did not reveal either in the aorta or in its vicinity any cause to which this extraordinary condition could be attributed.

The carotids and their branches showed nothing unusual. The innominate artery, the first branch of the arch, and also the subclavian, which arises from it, were a third larger than normal. The left subclavian artery was half again as thick as the normal. The branches of the two subclavians had increased in the same proportion and described extensive and multiple zigzags. The internal mammary arteries had a diameter of 2 lines (2.5 mm.), the superior phrenic had a diameter of $1^1/_2$ lines. The latter was very tortuous. The transverse cervicals were twice as thick as normal; all their posterior branches ran a long and sinuous course, and communicated with the posterior branches of the intercostals. The intercostals which arise from the subclavians had a diameter of 2 lines. The thoracic arteries, the common scapular, and the other principal branches which come from the axillary arteries to branch out wholly or partly on the chest were as large again as the normal.

The successive intercostal arteries which arose from the thoracic aorta below the narrowing were larger and larger the nearer one came to the constriction. The first and the second each had a diameter of 3 lines; the others diminished gradually and the last were almost normal. The anterior branches of these arteries were little enlarged but the posterior branches were so much enlarged and formed such intricate and closely approximated zigzags that they resembled the beads of a necklace placed one against another. Their communications with the transverse cervicals were large and very conspicuous.

The branches of the abdominal aorta were unremarkable except the inferior phrenic,

which was abnormally thick and presented large communications with the superior phrenic; likewise the epigastric artery, which was as thick as the internal mammary with which it had a large number of very distinct anastomoses.

From the circumstances which have just been described it is clear that in this woman the circulation worked in an extraordinary way. Instead of passing directly along the trunk of the aorta, the blood went from the branches which originated above the narrowing, i.e., those from the subclavian and axillary arteries, into the branches which arose below the narrowing, such as the intercostals, the inferior phrenics and the epigastrics, through the numerous communications which existed between these arteries, around the chest, and the anterior part of the abdomen.

M. Desault has preserved the specimen in his collection.

# Case Reports

## Aortic Anomaly with Atypical Coarctation

### A Report of Three Cases Presenting Coarctation between the Origin of the Left Carotid and the Left Subclavian Artery*

BENGT W. JOHANSSON, M.D, PAUL HALL, M.D., HANS KROOK, M.D., ARNE MALM, M.D., NILS-MAGNUS OHLSSON, M.D., LARS ANDRÉN, M.D. *and* HELGE B. WULFF, M.D.

Malmö, Sweden

COARCTATION OF THE AORTA is usually situated in the isthmic part, between the left subclavian artery and the insertion of the ductus arteriosus. Coarctations have also been described in other parts of the aorta; e.g., in the ascending part of the aorta[1,2] which may reveal total atresia, in the aortic arch between the origin of the right common trunk and a common origin of the left subclavian and common carotid artery,[3] between the origin of the left carotid artery and the left subclavian artery,[4–6] and, finally, the coarctation may be somewhere in the descending portion of the aorta.[7–9] Other arteries such as the renal vessels can show coarctations.[10] In some cases the big vessels leaving the aortic arch have an anomalous origin.[11,12] The aortic arch can have different degrees of hypoplasia.[13–15] Sometimes this arch is prolonged, so that the distance between the left common carotid and the left subclavian artery is strikingly long.[16] Dilatations due to aneurysm have been described,[6,16] as have multiple coarctations.[3,16] Arkin[17] and Edwards[18] have given a detailed account of the different possibilities of a faulty development of the aortic arch.

The following three cases are presented because they belong to groups of aortic anomalies seldom noted and because they might help to explain some of the very complicated embryologic development of this part of the cardiovascular system.

#### CASE REPORTS

CASE 1. The patient was a twenty-eight year old man. A hemangioma on the left half of his face was successfully treated at an early age. As a child he became more easily dyspneic on exertion than his playmates and sometimes noted a slight feeling of pressure in his chest. Two months before entering the hospital he became very dyspneic and experienced severe pain in the left side of the thorax after running for a bus. The symptoms disappeared rapidly after a few minutes rest.

There was no previous history of headache, coldness or swelling of the legs. He worked as a shipwright and carried on moderate exertion without cardiac symptoms.

*Physical examination* revealed a tall man without signs of cardiac decompensation. A systolic murmur was audible over the whole precordium, with maximal intensity (grade 4) in the left second intercostal space. The murmur was audible over the back, to the right of the sternum and over the carotids. The pulsations were much weaker in the left radial artery than in the right. The blood pressure was 170/75 mm. Hg in the right arm, 110/80 in the left arm, 140/105 in the right leg and 150/105 in the left leg.

*Teleroentgenogram* revealed a total heart volume of 750 ml. and a relative volume of 360 ml. per square meter of body surface.[19] The aortic arch was situated very high in the thorax. The *electrocardiogram* was within normal limits without signs of left ventricular hypertrophy; the electrical axis was normal and the electrical position was vertical. The *ballistocardiogram* revealed moderate changes of the type noted in coarctation of the aorta. At an ergometer *exercise test*

* From the Cardiological Laboratory, Department of Medicine, the Department of Thoracic Surgery and the Department of Roentgenology, General Hospital, Malmö, Sweden.

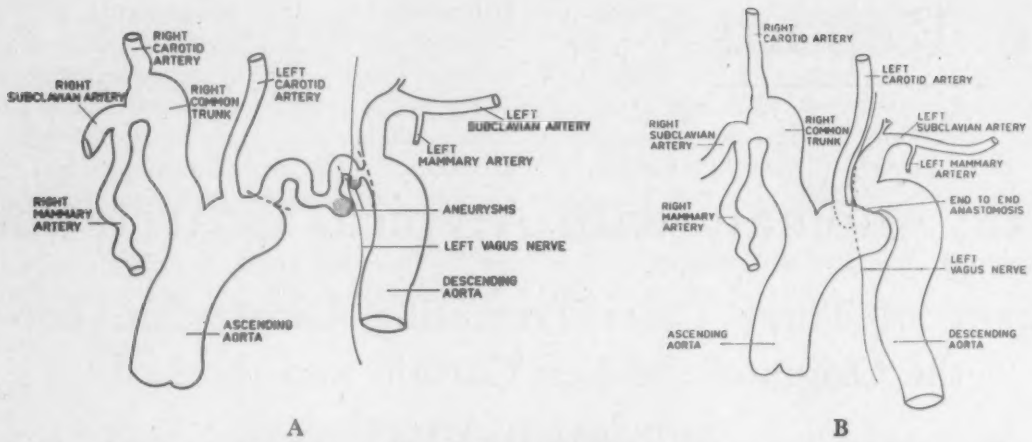



FIG. 1. Case 1. Drawing of anatomical findings at surgery. A, preoperative; B, postoperative.

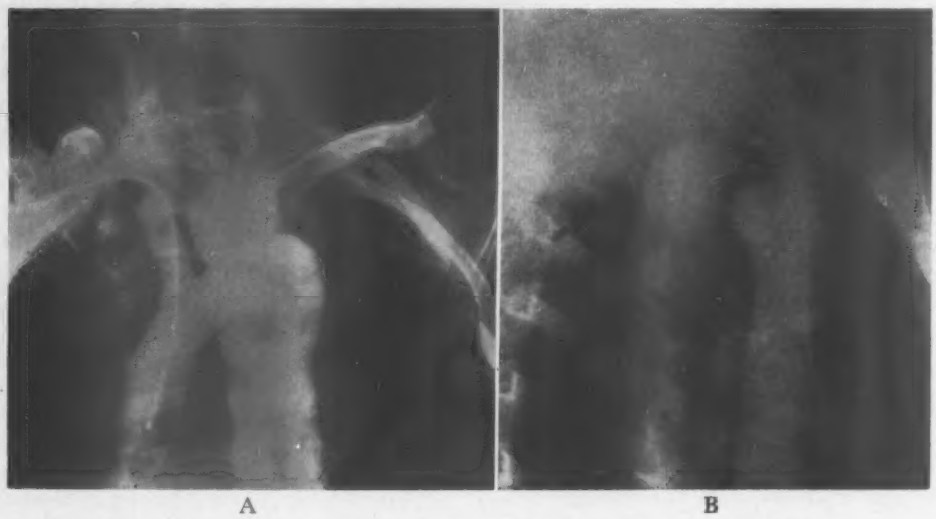



FIG. 2. Case 1. Postoperative aortography. A, frontal view; B, lateral view.

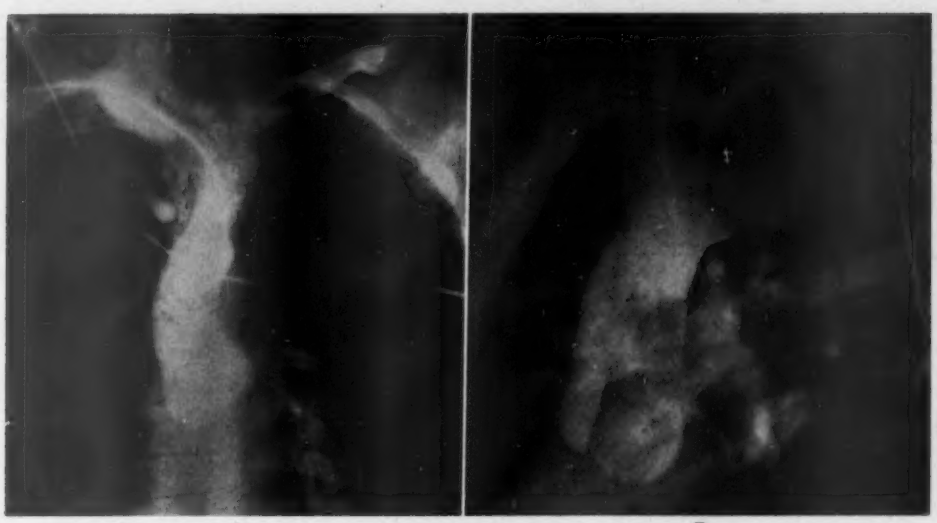
the patient showed a normal reaction as far as the pulse rate and the electrocardiogram were concerned but the respiratory rate and the blood pressure increased to supernormal values. A detailed *broncho-spirometric analysis* was within normal volumetric and ventilation limits.

A right-sided *cardiac catheterization* revealed normal pressures and no signs of arterial shunting. All blood values were within normal limits. Urinalysis also revealed normal values.

*Angiocardiography* with the contrast injection into the right chamber showed that the ascending aorta was somewhat dilated with signs of a coarctation of the aortic arch extending high up in the thorax as far as the upper border of the manubrium. *Thoracic aortographies* were performed, one via the right brachial artery with contrast injection into the ascending aorta, another via the femoral artery with injection into the proximal part of the descending aorta. Although it was not possible to get a clear picture of the S shaped narrowed part of the aortic "arch" these aortographies revealed that the origin of the right common trunk was normal, that distal to the right common trunk the aorta became tortuous with a slow contrast flow in this part and that after the tortuous, high-situated part of the aorta one big vessel emerged. Furthermore, the right internal mammary artery was wide and tortuous whereas no left internal mammary artery was visible.

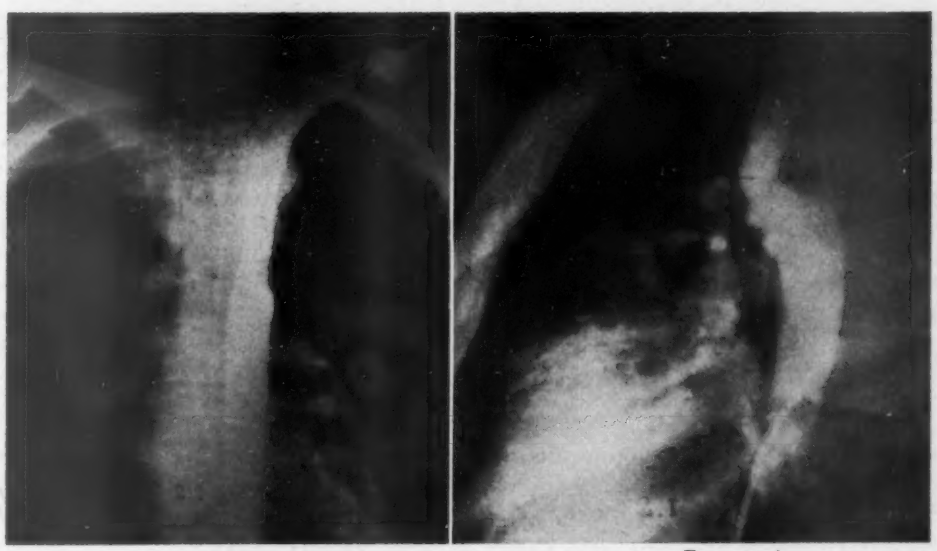
*Operative Findings and Results:* An operation was performed in hypothermia at a body temperature of 32.5° C. The anatomic picture at the operation is shown in Figure 1. There was an S or U shaped, rather narrow "aortic arch" with two aneurysms; one the size of a pea close to the origin of the left subclavian artery and a bigger one in the caudal part of the aortic arch. The tortuous part of the aortic arch, including the two aneurysms, was resected and an end to end anastomosis was performed. There was a marked thrill also after this anastomosis was made but the diameter of the aorta increased from about 14 mm. to about 20 mm.

The postoperative course was uneventful. One month after the operation the blood pressure was 140/80 mm. Hg in the right arm, 120/70 in the left arm, 150/100 in the right leg and 145/100 in the



A B

FIG. 3. Case 2. Preoperative aortography from above through the brachial artery. A, frontal view; B, lateral view.



A B

FIG. 4. Case 2. Preoperative aortography from below through the femoral artery. A, frontal view; B, lateral view.

left leg. There was still a systolic murmur over the whole precordium but of a lower intensity than before the operation (maximum intensity, grade 2 or 3). A postoperative aortography with contrast injection into the ascending part of the aorta revealed that the aortic segment between the left common carotid and left subclavian arteries was still somewhat narrowed. Furthermore, the left vertebral artery was not demonstrated in spite of very good visualization of the other vessels (Fig. 2).

CASE 2. This was a nineteen year old man who had always felt well and had been able to play football with no more symptoms than other boys of his own age. There was no previous history of headache or coldness in his feet or legs. He was hospitalized for further study because of a systolic murmur revealed at a routine examination.

*Physical examination* revealed a systolic thrill over the lower part of the right carotid artery and a systolic murmur over the whole precordium with maximal intensity (grade 4) in the left second interspace. The murmur was audible over the back but the intensity there was lower than over the precordium. No diastolic murmur was audible. Slight pulsations were noted over the right dorsal half of the thorax but not over the left. The blood pressure was 175/100 mm. Hg in the right arm, 120/100 in the left arm and 120/95 in the right and left legs. An eyeground examination revealed tortuous arteries and no hematomata.

An *electrocardiogram* showed high QRS amplitudes

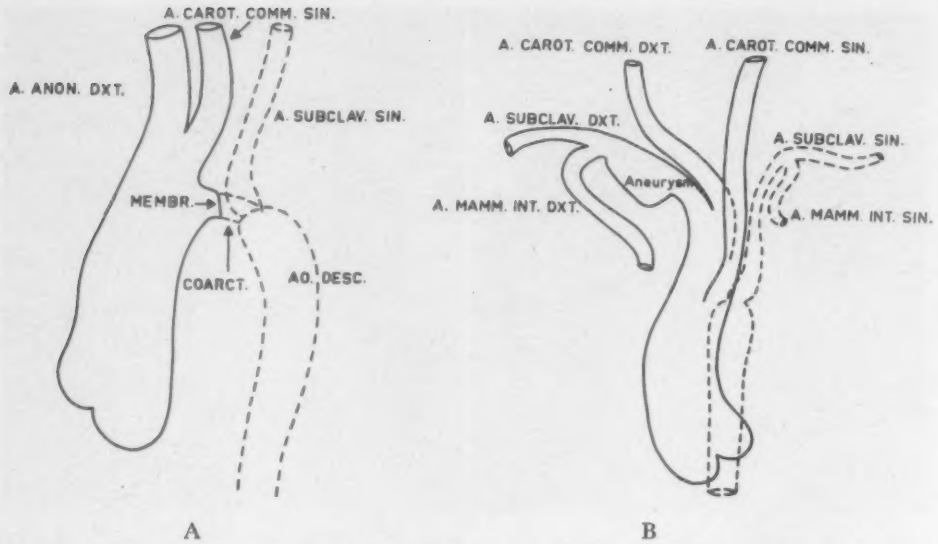



FIG. 5. Case 2. Drawing of anatomical findings at surgery. A, preoperative; B, postoperative.

in the precordial leads indicating incipient left ventricular hypertrophy. Teleroentgenogram revealed a normal relative heart volume of 380 cc. per square meter of body surface[19] with a slight prominence of the left ventricle. Slight notching of some ribs was noted on the right side.

*Aortography* was performed from below through the femoral artery and from above through the brachial artery (Figs. 3 and 4). The aortographies showed a normal ascending aorta ending in a common brachiocephalic trunk which divided into a wide right subclavian artery and a right common carotid. Two centimeters after its origin the right subclavian artery showed a coarctation; distal to this there was a poststenotic dilatation. A wide left common carotid artery emerged from the left dorsal part of the ascending aorta. The left subclavian and mammary arteries were filled from an ample collateral network in the neck. The aortic arch was almost completely atretic with a very small amount of contrast medium passing through it. The left subclavian artery had its origin at the descending part of the aorta (Fig. 5).

*Operative Findings and Results:* The clinical findings were confirmed at operation (Fig. 5). The coarctation was of the membranous type The narrowed part of the aorta was opened longitudinally and the membrane removed. Postoperative aortography with contrast injection into the ascending aorta showed an increased diameter at the place of the coarctation. The left subclavian artery was not only filled through the collaterals, as before the operation, but also directly from the aorta. The postoperative blood pressure values were 130/85 mm. Hg in the right arm, 110/80 in the left arm and 120/85 in both the right and left legs.

CASE 3. This patient was a five year old boy with a known systolic murmur since the age of four months. On one occasion he had been treated in the hospital because of anemia; at this time a coarctation of the aorta was suspected. He had no symptoms of cardiac disease. He was hospitalized for further studies of the vascular lesion.

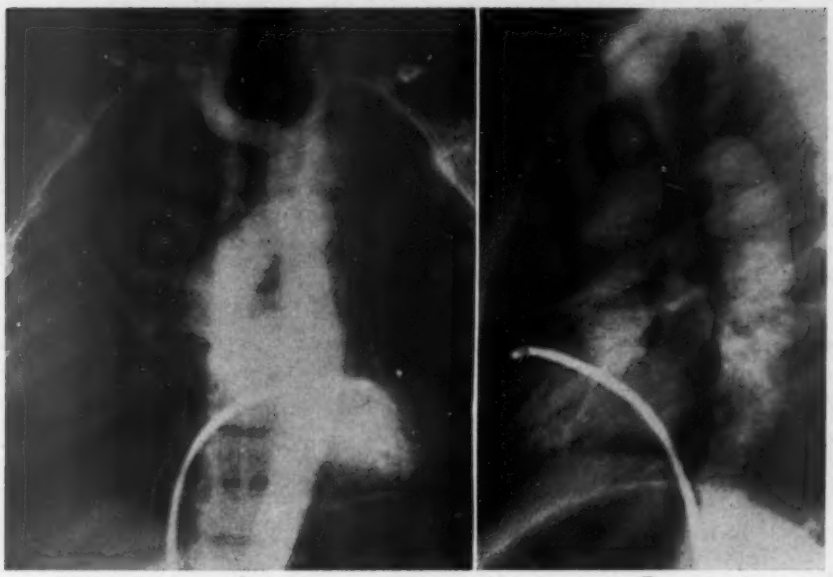
*Physical examination* revealed a systolic thrill over the basal part of the precordium; it was of an especially high intensity in the jugular notch. A systolic murmur was heard over the whole precordium and the back with maximal intensity (grade 6) in the aortic region. The blood pressure in the right arm was 110/70 mm. Hg, in the left arm 80/?, and in the legs 80/?. A twelve lead electrocardiogram was normal. X-ray examination of the chest revealed an abnormal aorta. A right *cardiac catheterization* showed normal pressures in the right heart and pulmonary artery and no signs of arterial shunting.

*Angiocardiography* with the injection into the right ventricle (Figs. 6 and 7) revealed normal heart chambers. The ascending aorta was slightly dilated and progressed high up into the thorax toward the upper part of the sternum, where it showed a pronounced bending just after the origin of the right brachiocephalic trunk and the left common carotid artery. The descending aorta had another bend after the origin of a dilated left subclavian artery. There are no indications at this time for surgical correction of the aortic anomaly as the patient feels well and has no hypertension.

## COMMENTS

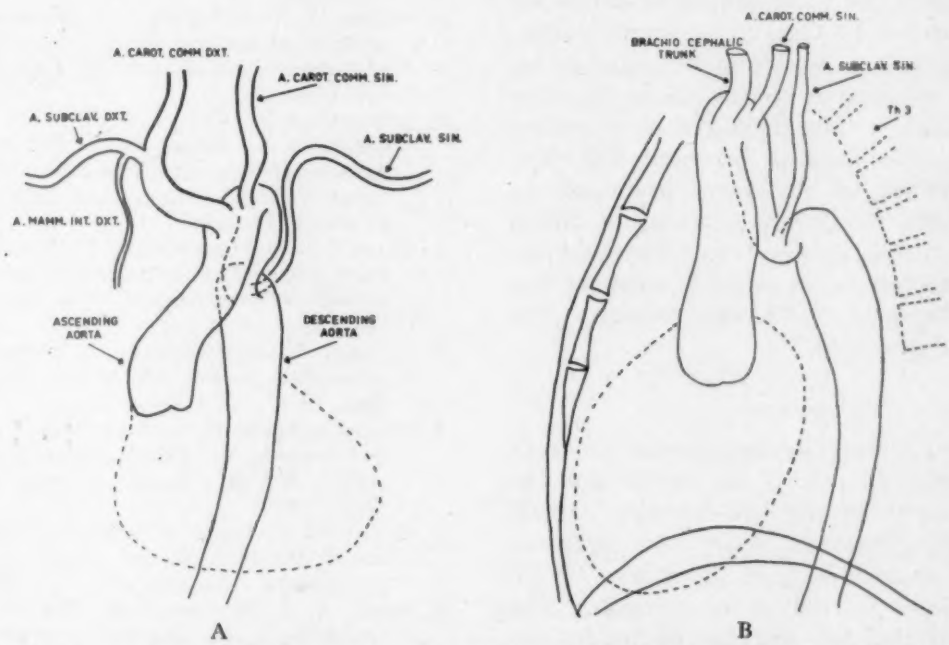
There is no agreement concerning the mechanism for the development of a congenital coarctation of the aorta. The two main theories are as follows:

1. *The so-called skodaic theory* was first formulated not by Skoda but by Craigie in 1841.[13] Furthermore, Skoda mentioned two possibilities



A B

FIG. 6. Case 3. Angiocardiography through the right ventricle. A, frontal view; B, lateral view.




A B

FIG. 7. Case 3. Diagrammatic representation of angiocardiographic findings. A, frontal view; B, lateral view.

when he wrote that there is either an obliteration of the aortic isthmus already during fetal life or the obliterating processes from the ductus arteriosus extend into the aorta.[20] The so-called skodaic theory holds that coarctation of the aorta is produced in a similar way by extension of the obliterative process from the ductus arteriosus into the aorta. This theory has been much criticized, one of the arguments being that the pulmonary artery never has a coarctation. This is not valid; coarctation of the pulmonary artery does exist[21] although it is uncommon. However, even if the skodaic theory is correct in some cases of coarctation it cannot be used as a general explanation. It will, for example, be very difficult with the help of this theory to explain the free distance observed in many cases between the coarctation and the insertion of the vessel from which the obliterating processes should have originated

2. *Coarctation is the result of faulty development.* According to Evans[13] this explanation was first suggested by Raynaud in 1828. This theory is the more probable one in coarctations situated some distance from the opening of the vessels that are obliterated before (branchial arteries) or after (ductus arteriosus) the parturition. Niedner[20] stresses the effect of tension on the aortic isthmus during fetal life, in a caudal direction by the ductus arteriosus at the descensus of the heart, and in a cranial direction by the subclavian artery. This tension in opposite directions produces a narrowing of the aorta which, according to Thérémin,[22] persists in 80 per cent of all infants up to an age of three months. Doerr[23] points out that this narrowing of the aortic isthmus is not found during the first quarter of fetal life and does not begin until the subclavian artery has moved.

The multiple defects in the first case with a tortuous and aneurysmatic coarctation make it probable that a faulty development produced this coarctation. In Case 2 the main pathologic finding was a membranous coarctation; in this case the skodaic theory might be more easily applicable. Case 3 showed no anatomic coarctation; functionally, however, the pronounced bending of the aorta produced an obstacle for the blood flow resulting in differences in the blood pressure before and after the bending. A similar case of aortic anomaly, but without differences in blood pressure, has recently been described.[24]

## Summary

Three cases of faulty development of the aorta are presented. In Case 1 the aortic arch between the origin of the left common carotid and the left subclavian artery was tortuous, narrow and situated high in the thorax. Two aneurysms were located in this portion. The left vertebral and left internal mammary arteries were not demonstrated. The narrowed part of the aorta was resected under hypothermia with a good result.

Case 2 showed a pronounced coarctation between the left common carotid artery and the left subclavian artery. This latter vessel was filled almost completely via an ample collateral network. The left common carotid artery had an anomalous origin and the right subclavian artery showed a slight coarctation in the proximal part; a poststenotic dilatation was distal to this.

Case 3 showed an aortic arch situated high in the thorax. The bending of the aortic arch was very sharp, producing a functional coarctation with differences in the blood pressures in the right and left arm; there was no anatomic coarctation in the ordinary sense.

Two cases were corrected by surgery; the former by resection of the tortuous part and end to end anastomosis, the latter by incision and removal of the membrane.

The different theories concerning the development of coarctation of the aorta are discussed. It is suggested that the cases presented might best be explained by faulty development.

## References

1. Eiken, M. Coarctation of the aorta. Atypical localization central to the origin of the innominate artery. *Acta med. Scandinav.*, 165: 235, 1959.
2. Denie, I. J. and Verheugt, A. P. Supravalvular aortic stenosis. *Circulation*, 18: 902, 1958.
3. Efskind, L. and Sanderud, A. An unusual case of coarctation of the aorta. *J. Thoracic Surg.*, 29: 665, 1955.
4. Parker, R. L. and Dry, T. J. Coarctation of the aorta at an unusual site, associated with a congenitally bicuspid aortic valve. *Am. Heart J.*, 15: 739, 1938.
5. Edwards, J. E., Dry, T. J., Parker, R. L., Burchell, H. B., Wood, E. and Bulbulian, A. H. An Atlas of Congenital Anomalies of the Heart and Great Vessels, p. 139. Springfield, Ill., 1954. Charles C Thomas.
6. Ellis, F. H. and Clagett, O. T. Coarctation of the aorta proximal to the left subclavian artery: experience with six surgical cases. *Ann. Surg.*, 146: 145, 1957.
7. Loogen, F. and Wetzels, E. Stenose der absteigenden Aorta. *Ztschr. Kreislaufforsch.*, 47: 1061, 1958.
8. Hansson, J., Ikkos, D., Johansson, L., Rudhe, U. and Senning, Å. Coarctation of the abdominal aorta. *Acta chir. Scandinav.* (suppl.), 245: 315, 1959.
9. Zaroff, L. J., Kreel, I., Sobel, H. J. and Baronofsky, I. D. Multiple and intraductal coarctation of the aorta. *Circulation*, 20: 910, 1959.
10. Brust, A. A., Howard, J. M., Bryant, M. R. and Goodwin, J. T. Coarctation of the abdominal aorta with stenosis of the renal arteries and hypertension. *Am. J. Med.*, 27: 793, 1959.
11. Brynolf, I., Crafoord, C. and Mannheimer, E. Coarctation of the aorta proximal to both subclavian arteries. *J. Thoracic Surg.*, 35: 123, 1958.
12. McGregor, M. and Medalie, M. Coarctation of the aorta. *Brit. Heart J.*, 14: 531, 1952.
13. Evans, W. Congenital stenosis (coarctation), atresia and interruption of the aortic arch. *Quart. J. Med.*, 26: 1, 1933.
14. Marston, E. L., Bradshaw, H. H. and Meredith, J. H. Agenesis of the aortic isthmus. *Surgery*, 42: 352, 1957.
15. Lev, M. Autopsy Diagnosis of Congenitally Malformed Hearts, p. 58. Springfield, Ill., 1953. Charles C Thomas.

16. KARNELL, J., CRAFOORD, C. and BRODÉN, B. In: Handbuch der Thoraxchirurgie, vol. II, p. 365. Edited by Derra, E. Berlin, 1959. Springer Verlag.
17. ARKIN, A. Double aortic arch with total persistence of the right and isthmus stenosis of the left arch: a new clinical and x-ray picture. *Am. Heart J.*, 11: 444, 1936.
18. EDWARDS, J. E. Anomalies of the derivatives of the aortic arch system. *Med. Clin. North America*, 32: 925, 1948.
19. LILJESTRAND, G., LYSHOLM, E., NYLIN, G. and ZACHRISSON, C-G. The normal heart volume in man. *Am. Heart J.*, 17: 406, 1939.
20. NIEDNER, F. F. Bemerkungen zur Entstehung und Auswirkung der Aortenisthmusstenose und zu ihrer Abgrenzung gegen Aortenisthmus-Hypoplasie und Aplasie. *Thoraxchirurgie*, 5: 213, 1957.
21. HALL, P., JOHANSSON, B., KROOK, H., MALM, A., OLSSON, N.-M., ANDRÉN, L. and WULFF, H. B. Coarctation of the pulmonary artery and pulmonary valvular stenosis. A case report. *Am. J. Cardiol.* In press.
22. THÉRÉMIN, E. Cited in reference 20.
23. DOERR, W. Cited in reference 20.
24. ŠARIĆ, S., VULETIĆ, V., GVOZDANOVIĆ, V. and MARK, B. A case of kinking of the aortic arch. *Circulation*, 21: 1147, 1960.

# Muscular Subaortic Stenosis*

GEORGES DAOUD, M.D., MARIAN E. GALLAHER, M.D. *and* SAMUEL KAPLAN, M.D.

Cincinnati, Ohio

FOLLOWING THE ADVENT of surgical treatment of aortic stenosis,[1,2] left heart catheterization to measure the systolic gradient across the aortic valve has become a widely used technic. This procedure has led to the recognition of a new clinical entity consisting of a muscular obstruction to the outflow as a part of generalized ventricular hypertrophy with a resultant measurable systolic gradient between the left ventricle and aorta. In this condition the classic pathologic findings of supra-aortic,[3] aortic[4] or subaortic[5] stenosis are absent. This disease has been previously described as functional aortic stenosis,[6] functional obstruction of the left ventricle,[7,8] pseudo-aortic stenosis due to ventricular hypertrophy[9] and familial muscular subaortic stenosis.[10]

The purpose of this paper is to report a case of obstructive ventricular hypertrophy involving both ventricles with dominance on the left side, proved at autopsy, and to review similar cases from the literature. To our knowledge the case reported herein is the youngest patient described to date.

## CASE REPORT

A one year old white boy was admitted to the Cincinnati Children's Hospital for the removal of a dermoid cyst of the left eyelid which had been present since the age of two months. He was the product of a full term, uncomplicated pregnancy and a normal delivery. His weight at birth was eight pounds fourteen ounces. He had one sibling, aged two years, who was in good health. The family history was unremarkable, particularly in reference to the cardiovascular system. The child's development was normal and he had been considered to be in good health. The parents were unaware of the presence of a heart murmur.

*Physical examination* revealed a well developed, somewhat small child, weighing nineteen pounds. He was afebrile and acyanotic. The blood pressure was 95/65 mm. Hg in his arms and 105/60 mm. Hg in his legs. He was in no apparent distress. No rales or wheezes were heard in the lungs. The heart was moderately enlarged, with a sinus rhythm and a rate of 96 beats per minute. There were no palpable thrills. On auscultation, there was a grade 3 systolic murmur, ejection in type, best heard in the second intercostal space to the right of the sternum. It was well transmitted down the left sternal border but only poorly into the neck. No diastolic murmur was heard. The second sound in the pulmonic area was single and loud. The liver was palpable 5 cm. below the right costal margin.

*The electrocardiogram* revealed evidence of left ventricular hypertrophy (Fig. 1). Examination of the blood revealed a hemoglobin of 11.5 gm. per 100 ml. and a white blood cell count of 12,800 per cu. mm. with a normal differential distribution. *Roentgenographic examination* of the chest revealed moderate cardiomegaly with prominence of the ascending aorta and main pulmonary artery and normal intrapulmonary vasculature (Fig. 2).

*Cardiac Catheterization:* Because of the character of the murmur, the electrocardiographic evidence of left ventricular hypertrophy and the signs of heart failure, the clinical diagnosis was severe congenital aortic stenosis. After digitalization left heart catheterization was undertaken under general anesthesia. The left ventricle was entered by percutaneous puncture. Simultaneous pressures were recorded from the ascending aorta and left ventricle. The arterial pressure was 65/48 mm. Hg and the left ventricular pressure was 105/25 mm. Hg (Fig. 3). The cardiac output was not measured. It was believed that the 40 mm. Hg systolic gradient across the aortic valve was due to severe aortic stenosis with congestive heart failure and probable low cardiac output.

*Operative Findings:* Surgery was undertaken using total body perfusion. During thoracotomy, muscular hypertrophy of both ventricles, particularly the left, was striking. There was dilatation of both the ascending aorta and the main pulmonary artery; a systolic thrill was easily felt in both arteries. With the chest open a recording of the pulmonary arterial and right ventricular pressures demonstrated a systolic gradient of 35 mm. Hg. During cardiac asystole, induced by potassium citrate, the aortic valve and the left ventricular outflow tract were examined

* From the Department of Pediatrics, Children's Hospital Research Foundation, College of Medicine, Cincinnati, Ohio. This work was supported in part by a training grant (HTS-5371) from the National Heart Institute, National Institutes of Health.

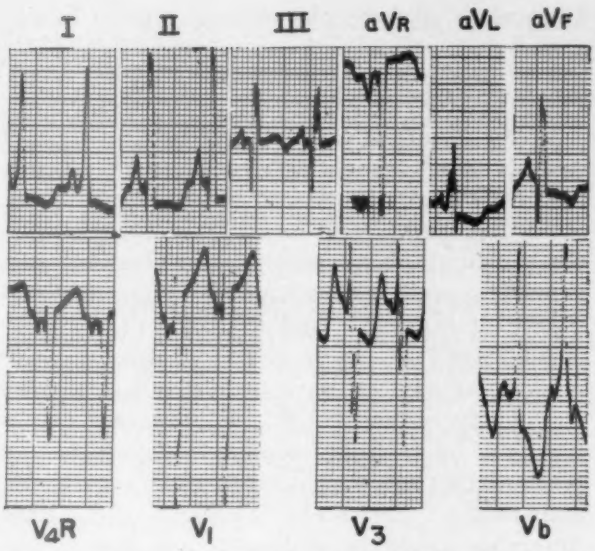



FIG. 1. Electrocardiogram before digitalization showing tall spiked P waves, short P-R interval, and severe left ventricular hypertrophy. An intraventricular conduction disturbance is not excluded.

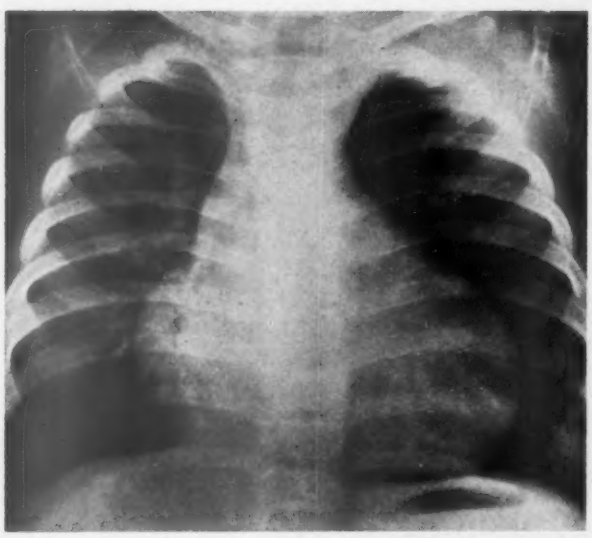


FIG. 2. Posteroanterior teleoroentgenogram (see text).

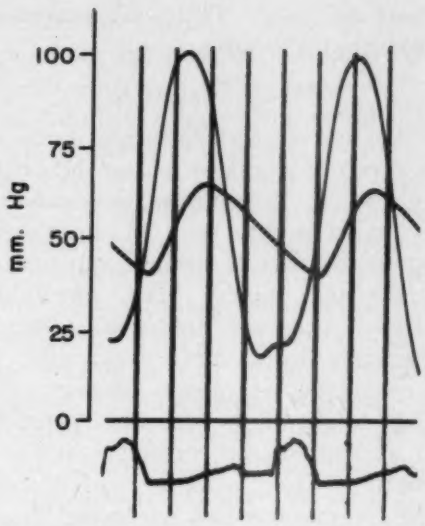



FIG. 3. Simultaneous pressure recordings from the left ventricle and the ascending aorta. The lower tracing is the electrocardiogram.

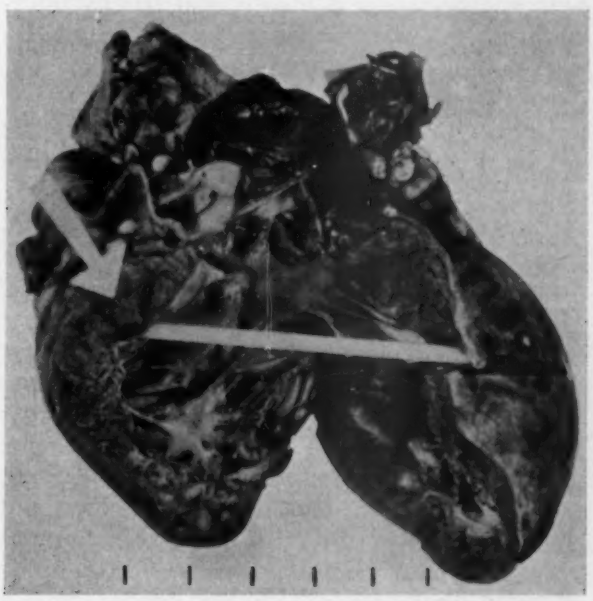


FIG. 4. Specimen showing the opened left ventricle and ascending aorta. Arrow indicates the site of the subaortic muscular hypertrophy.

through an aortotomy. The pulmonary valve and infundibular chamber were examined through a right ventriculotomy. The valves were within normal limits and no obstructive lesion was noted in the outflow of either ventricle. The patient died five hours after operation.

*Autopsy Findings:* The heart weighed 92.5 gm. (normal for age is 44 gm.). Muscular hypertrophy of both ventricles, more marked on the left, was noted. The left ventricular myocardium was grossly but variably thickened. The area of maximal thickening formed a ring of muscular tissue immediately below the aortic valve (Fig. 4). The myocardium was dark, thickened and firm but not fibrotic. All the valves including the aortic were flexible, translucent and normally formed. There was no evidence of supravalvular or subvalvular aortic stenosis. Endocardial fibroelastosis was not present. The outflow tract of the right ventricle was normally formed. There were no septal defects and the coronary arteries were not remarkable. The thickness of the left ventricle varied from 1.5 to 0.75 cm.; that of the right ventricle was 0.75 cm.

Microscopically, the myocardial fibers were thick with large, blunt, elongated nuclei. The endocardium was not thickened and there was no evidence of myocardial fibrosis or necrosis. The myocardial blood vessels had duplicate internal elastic membranes

which were thickened. The media in some of these vessels was also thickened.

### Comments

This boy had clinical features of aortic stenosis with a pressure gradient across the outflow of both ventricles. At autopsy, generalized myocardial hypertrophy with a muscular ring causing obstruction of the left ventricular outflow tract was noted. The mechanism of hypertrophy was not apparent. There were no detectable intra- or extracardiac lesions. Anemia, cardiac glycogen storage disease,[11] abnormal origin of the coronary arteries[12] and medial sclerosis of the coronary arteries[13] were not present. There was no evidence of myocarditis[14] or endocardial sclerosis.[15,16] Hypertension was not present. There was no familial history of ventricular hypertrophy and the histologic picture of familial hypertrophy with vacuolization of muscle and patchy interstitial fibrosis was not found.[17] The only striking pathologic finding was ventricular hypertrophy of unknown cause.

Congenital idiopathic myocardial hypertrophy frequently presents a clinical picture characterized by dyspnea, tachypnea, cyanosis, intractable heart failure and ultimate death. Specific heart murmurs are usually absent and dilatation of the heart is a common finding.[18,19] However, a significant heart murmur may be present and, as in our case, may simulate valvular stenosis. Variable clinical pictures have also been reported in idiopathic myocardial hypertrophy in adults. The signs may be those of tachycardia, arrhythmia, peripheral emboli, pain in the chest and heart failure without significant murmurs.[20,21] However, patients may have the clinical picture of rheumatic valvular heart disease.[22] Some of these patients have been subjected to mitral valvotomy only to find normal valves and idiopathic ventricular hypertrophy.[23]

In our patient the suggested diagnosis was congenital idiopathic hypertrophy because the known causes of ventricular hypertrophy were excluded. On the other hand, instead of being "idiopathic" the muscular hypertrophy in the left ventricular outflow tract might represent a a developmental anomaly and possibly be related to the asymmetric hypertrophy described by Teare.[24] This entity has presented clinical features not unlike aortic stenosis; however, the bizarre arrangement of bundles of muscle separated by connective tissue described in asymmetric hypertrophy was not present in our case.

### Review of Literature

In all reported cases of muscular subaortic stenosis the clinical features were suggestive of valvular aortic stenosis and the only abnormal finding at surgery or autopsy was the ventricular hypertrophy. In general, both ventricles were hypertrophied with predominance of the left. The thickness of the ventricular wall has been at least 2 cm. and the ventricular cavities have been small or almost completely obliterated.[9,10] In our case, however, the hypertrophy was predominant at the outflow tract and the thickness of the ventricular wall was 1.5 cm. at its maximum site. This difference could be related to the age of the patient.

The microscopic studies have not helped in the evaluation of the cause of the condition and only hypertrophy of the individual fibers with minimal subendocardial fibrosis was noted. It is noteworthy that our case demonstrated the arterial medial hypertrophy described by DeMuth and Landing[25] in congenital idiopathic hypertrophy.

Muscular obstruction of the left ventricular outflow was apparent in several instances. In others, no obstruction was found in the arrested heart during surgery to explain the measured systolic gradient between the left ventricle and the aorta. Morrow[6] demonstrated by selective angiocardiography that in these cases the obstruction is present during ventricular systole. In our case the gradient measured was most likely a consequence of the muscular obstruction of the left ventricular outflow tract with a functional component during systole. This mechanism would also explain the gradient recorded at the pulmonic outflow tract. We are not aware of any report in which ventricular hypertrophy has simulated isolated pulmonic stenosis.

### Etiology

The suggested causes of the ventricular hypertrophy in the above mentioned cases have been various. Bercu et al.[9] have indicated that the hypertrophy is familial and Brent et al.[10] suggested that the anomaly is inherited by mendelian dominance. In his early studies, Brock[7] emphasized the role of hypertension in the causation of this disease. He was unable to confirm this hypothesis in his later observations and suggested his patients also fall into the

group of idiopathic muscular hypertrophy.[8] Idiopathic left ventricular hypertrophy was suggested as the cause in Morrow's cases.[6] We believe that the pathogenesis is at present unknown, but from our case we suggest the possibility of a developmental anomaly of the ventricular outflow tract.

DIAGNOSIS

The difficulty in diagnosing aortic obstruction produced by myocardial hypertrophy of the outflow tract and differentiating it from aortic valvular, subvalvular or supravalvular stenosis is manifest from the fact that the majority of cases described in the literature have been misdiagnosed. It has been suggested that left ventricular outflow obstruction could be suspected if the thrill and ejection systolic murmur were localized to the left sternal border or apex with poor transmission to the neck and if a diastolic murmur were absent.[6,9,10] However, these features are not constant. Brock's[7] patient had a basal systolic thrill and murmur and our patient had a systolic murmur, also maximal at the base. However, there have been no reported cases of functional muscular obstruction in the ventricle with a diastolic murmur. Poststenotic dilatation of the aorta was not found in some cases and its absence was thought to be a good differential point against congenital subaortic stenosis.[6] However, marked poststenotic dilatation was reported in some of Brock's[7] cases, and in our patient; although there was only a suggestion of it in x-ray films, dilatation of the aorta and pulmonary artery was obvious at surgery. Roentgenographic evidence of calcification in the aortic valve makes the diagnosis of aortic stenosis mandatory.

A withdrawal pressure curve from the aorta to the left ventricle revealing an intermediate zone of low pressure indicates the subvalvular location of the obstruction. Widened bisferiens pulse of the central aortic pulse has been recorded in one patient. This patient proved at autopsy to have muscular aortic stenosis and this pulse was thought to be of some diagnostic significance.[10] Selective left ventricular angiocardiography may yield information whereby obstructive ventricular hypertrophy could be suspected. This technic shows the thickness of the left ventricular wall, the encroachment in the cavity of the left ventricle and the site of obstruction.[6,26]

*Diagnosis of functional muscular obstruction of the left ventricular outflow tract* is of extreme importance because the condition is inoperable and exploratory thoracotomy has been extremely hazardous. On the other hand, its differentiation from valvular or subvalvular stenosis is mandatory because surgery is of known value in these cases.[1,2,27] The fact that each case of functional muscular aortic stenosis has presented atypical features of classic aortic stenosis does not simplify its diagnosis as these features could be present in valvular and subvalvular aortic stenosis. The possibility of functional aortic stenosis or at least the atypical nature of a case should be considered when any of the following features are noted: (1) low localization of the systolic murmur with poor transmission to the neck; (2) absence of a diastolic murmur; and (3) absence of poststenotic dilatation of the aorta. We have learned to be extremely cautious in such atypical cases, especially if surgery is contemplated. Additional investigation such as excluding the possibility of calcification in the aortic valve, attempting to obtain a withdrawal pressure from the aorta to the left ventricle, and performing selective left ventricular angiocardiography, should be undertaken in order to recognize the nature of the obstruction. Suspected cases of functional aortic stenosis in which surgery was deferred have been reported. Follow-up studies of these patients will be of great interest.

Functional muscular obstruction of the outflow tract of the left ventricle has only recently been emphasized. Because the diagnosis may be missed both at the operating table and at autopsy, the few cases reported probably do not indicate its true incidence. As emphasized previously, the clinical features have not been uniform. The only constant findings have been myocardial hypertrophy and a pressure gradient at the aortic valve. The hypertrophy involves the left ventricle predominantly and is usually out of proportion to the degree of obstruction.

It is not known whether the cases commented upon in this paper represent a single clinical pathologic entity. The proposed causes are at best only hypothetical at this time. Whether or not these cases are in any way related to other cases of ventricular hypertrophy not producing obstruction is uncertain.

## Summary

A boy one year of age presented the features of aortic stenosis with a systolic gradient of 40 mm. Hg across the aortic valve. At surgery

with the chest open a systolic gradient of 35 mm. Hg was measured across the pulmonic valve. No operable lesion was found. The child died postoperatively.

Autopsy revealed striking ventricular hypertrophy and a ring of muscular hypertrophy obstructing the outflow of the left ventricle. The right ventricle was normally formed. The suggested diagnosis was congenital idiopathic hypertrophy and its relation to asymmetric hypertrophy was raised.

Similar reported cases are reviewed. The difficulty and importance of differentiating muscular subaortic stenosis from congenital aortic and subaortic stenosis are stressed.

## References


1. Swan, H., Wilkinson, R. and Blount, S. G. Visual repair of congenital aortic stenosis during hypothermia. *J. Thoracic Surg.*, 35: 139, 1958.
2. Morrow, A., Sharp, E. and Braunwald, E. Congenital aortic stenosis: clinical and hemodynamic findings, surgical technique and results of operation. *Circulation*, 18: 1091, 1958.
3. Denie, J. J. and Verheught, A. P. Supra-valvular aortic stenosis. *Circulation*, 18: 902, 1958.
4. Edwards, J. E. Aortic stenosis. In: Pathology of the Heart, p. 409. Edited by Gould, W. E., Springfield, 1960. Charles C Thomas.
5. Saphir, O. Subaortic stenosis. In: Pathology of the Heart, p. 769. Edited by Gould, W. E. Springfield, 1960. Charles C Thomas.
6. Morrow, A. and Braunwald, E. Functional aortic stenosis. A malformation characterized by resistance to left ventricular outflow without anatomic obstruction. *Circulation*, 20: 181, 1959.
7. Brock, R. Acquired aortic subvalvular stenosis. Functional obstruction of the left ventricle. *Guy's Hosp. Rep.*, 106: 221, 1957.
8. Brock, R. Acquired aortic sub-valvular stenosis. Functional obstruction of the left ventricle. *Guy's Hosp. Rep.*, 108: 126, 1959.
9. Bercu, B. A., Diettert, G. A., Danforth, W. H., Pund, E. E., Jr., Ahlvin, R. C. and Belliveau, R. R. Pseudoaortic stenosis produced by ventricular hypertrophy. *Am. J. Med.*, 25: 814, 1958.
10. Brent, L. B., Aburano, A., Fisher, D. L., Moran, T. J., Meyers, J. D. and Taylor, W. J. Familial muscular subaortic stenosis: an unrecognized form of "idiopathic heart disease" with clinical and autopsy observation. *Circulation*, 21: 167, 1960.
11. Landing, B. H. and Bangle, R. Familial cardiac glycogen storage disease. Report of 2 cases and discussion of relation to other forms of abnormal glycogen deposition. *Bull. Internat. M. Mus.*, 31: 84, 1950.
12. Lyon, R. A., Johansman, R. J. and Dodd, K. Anomalous origin of the left coronary artery. *Am. J. Dis. Child.*, 72: 675, 1946.
13. Kissane, R. W. and Fidler, R. S. Congenital medial sclerosis of the coronary artery. *Am. Heart J.*, 7: 133, 1931.
14. Kenney, F. E. and Sanes, S. Dilatation and hypertrophy of the heart in infancy due to parenchymatous myocarditis. *J. Pediat.*, 3: 321, 1933.
15. Craig, J. M. Congenital endocardial sclerosis. *Bull Internat. M. Mus.*, 30: 15, 1949.
16. Dimond, E. G., Allen, F. and Moriarity, R. The clinical picture of endocardial fibroelastosis, infantile and childhood type. *Am. Heart J.*, 50: 651, 1955.
17. Campbell, M. and Warwick, M. Two more families with cardiomegaly. *Brit. Heart J.*, 13: 393, 1956.
18. Kugel, M. A. and Stoloff, E. Dilatation and hypertrophy of the heart in infants and in young children with myocardial degeneration and fibrosis (so called congenital idiopathic hypertrophy). *Am. J. Dis. Child.*, 45: 828, 1933.
19. McGill, H. C., Jr. and Thatcher, J. L. Unexplained hypertrophy in infants and children. *J. Louisiana State M. Soc.*, 107: 233, 1955.
20. Serbin, R. A. and Chojnacki, B. Idiopathic cardiac hypertrophy. Report of 3 cases. *New England J. Med.*, 252: 10, 1955.
21. Elster, S. K., Horn, H. and Tuchman, L. R. Cardiac hypertrophy and insufficiency of unknown etiology. *Am. J. Med.*, 18: 900, 1955.
22. Levin, E. B. and Cohen, S. L. Idiopathic myocardial hypertrophy simulating rheumatic heart disease. *Am. Heart J.*, 48: 637, 1954.
23. Spodick, D. H. and Littman, D. Idiopathic myocardial hypertrophy. *Am. J. Cardiol.*, 1: 610, 1958.
24. Teare, D. Asymmetrical hypertrophy of the heart in young adults. *Brit. Heart J.*, 20: 2, 1958.
25. DeMuth, G. R. and Landing, B. H. The occurrence and possible significance of generalized vascular disease in idiopathic cardiac hypertrophy. *Am. Heart J.*, 50: 643, 1955.
26. Bjork, V. O., Jonsson, B. and Nordenstrom, B. Subaortic stenosis. *Thorax*, 13: 201, 1958.
27. Brock, R. Aortic sub-valvular stenosis. Surgical treatment. *Guy's Hosp. Rep.*, 108: 144, 1959.

# Stenotic Involvement of All Four Heart Valves

## Report of Three Cases*

OSMAN GIALLORETO, M.D., F.A.C.C., NICHOLAS AÉRICHIDÉ, M.D. *and* P. P. ALLARD, M.D.

Montreal, Canada

THE VALVULAR SEQUELAE of rheumatic heart disease are usually different on the four valves in spite of identical supportive tissue and the same endothelial lining. It is likely that the valvular morphology, the dynamics and the pressures to which each valvular apparatus is subjected are factors in the determination of the lesions. They are encountered frequently at the mitral orifice and relatively less often at the aortic and tricuspid valves. Pulmonic valve involvement is, on the other hand, very rare and the lesion that significantly compromises its function is almost a curiosity.

Reviewing 1,000 cases of rheumatic cardiopathies, of which 176 had autopsy confirmation, Chavez et al.[1] did not find a single case with pulmonary valve involvement. Herrmann[2] reported five cases of pulmonary valvulitis among 4,776 necropsies carried out at the Charity Hospital in New Orleans. These observations stress the rarity of the panvalvular lesion first described by Coupland.[3] In 1909, Newton Pitt[4] described a case of quadristenosis; the pulmonary stenosis was thought to be congenital in orgin because of the presence of a poststenotic dilation. In 1937, McGuire and McNamara[5] published three cases with panvalvular lesions showing different degrees of stenosis. Pericarditis with recent valvular involvement was present in one of their patients. More recently, Evans[6] described the case of a forty year old patient who died with anasarca. Cardiac catheterization revealed the presence of pulmonary stenosis and the three other stenoses suspected clinically were found at necropsy. We had the occasion to see, during the past six years, three patients with quadristenosis. Antemortem diagnosis was established in two of these cases.

### CASE REPORTS

CASE 1. G. E. G., a twenty-eight year old white woman, was referred to the Montreal Institute of Cardiology in July 1954 because of valvular heart disease and intractable cardiac failure. She had suffered from acute rheumatic fever at the age of eighteen years, followed by several annual relapses. Up to age twenty she led a completely normal life and was able to practice sports such as skiing and skating. Subsequently, at the age of approximately twenty-one years, she began to experience exertional dyspnea but this remained mild enough for the next six years to allow her to do heavy housework. She married in September 1953, at twenty-seven years of age. One month later, her exertional dyspnea suddenly increased and she noted for the first time the ap-

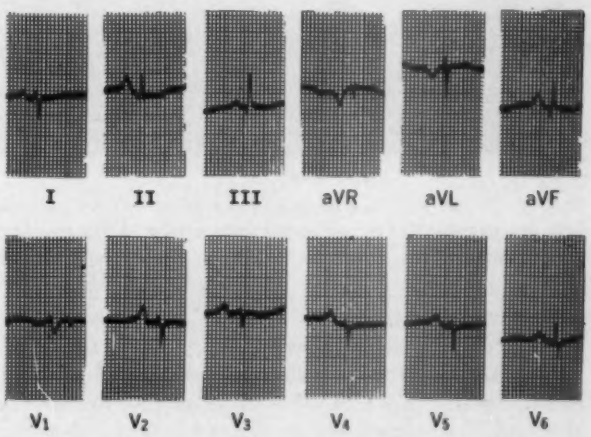
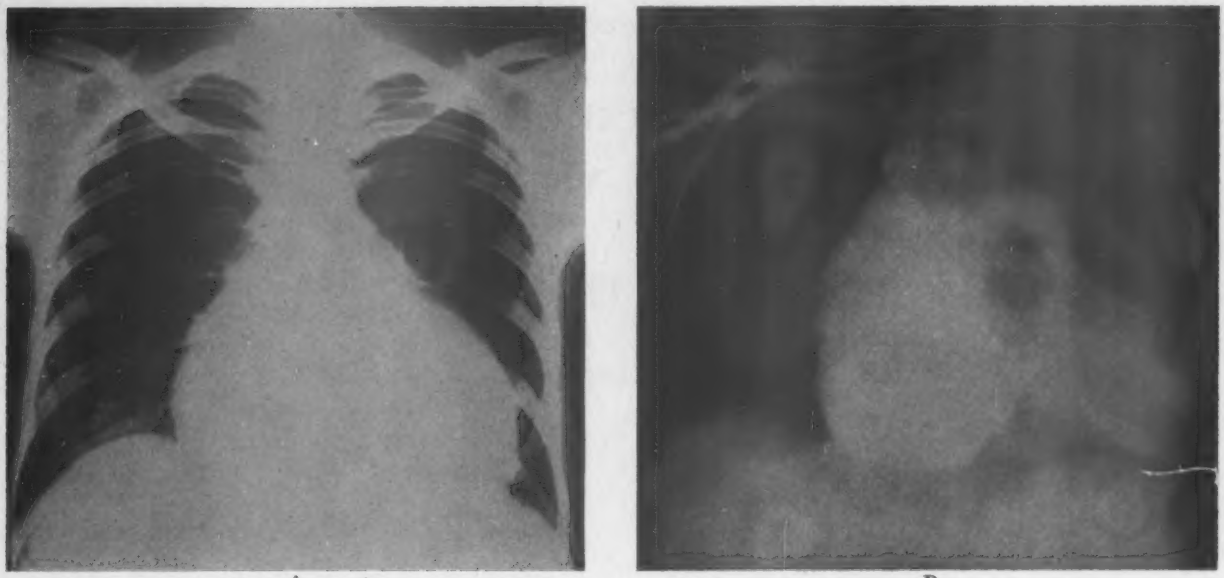


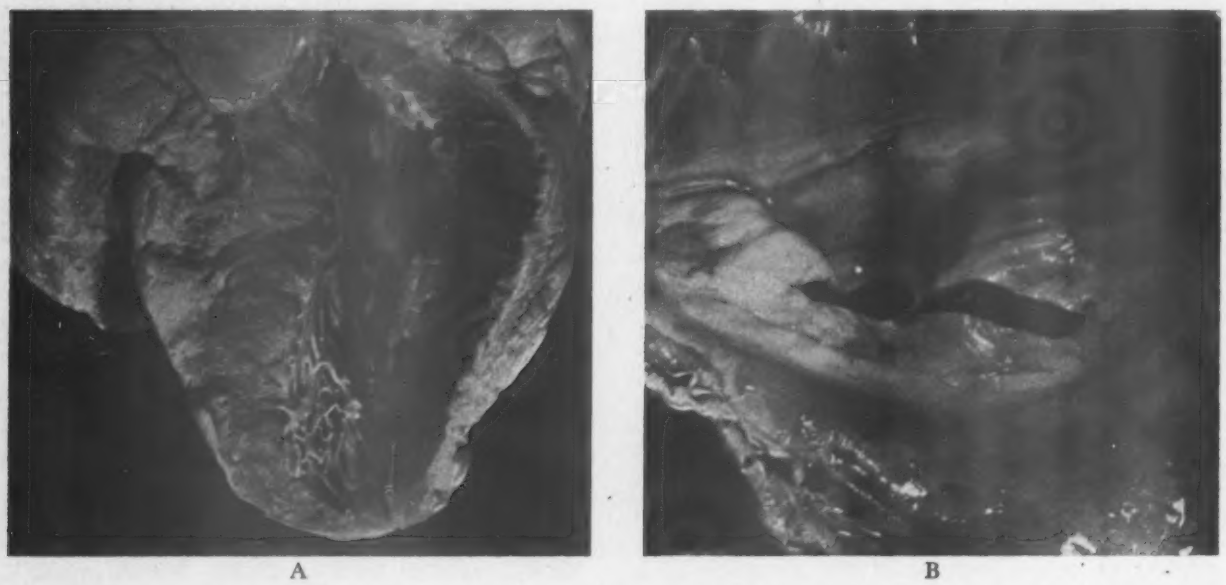

FIG. 1. Case 1. Electrocardiogram showing biauricular hypertrophy, right ventricular hypertrophy and QRS complexes of low voltage compatible with pericardial effusion.

* From the Montreal Institute of Cardiology, Montreal, Canada.



A B

FIG. 2. Case 1. A, roentgenogram showing greatly enlarged cardiac shadow and configuration compatible with pericardial effusion. Note diminished pulmonary vascular markings. B, angiocardiogram showing delayed opacification of enormous right atrium and diminished pulmonary vascular markings.

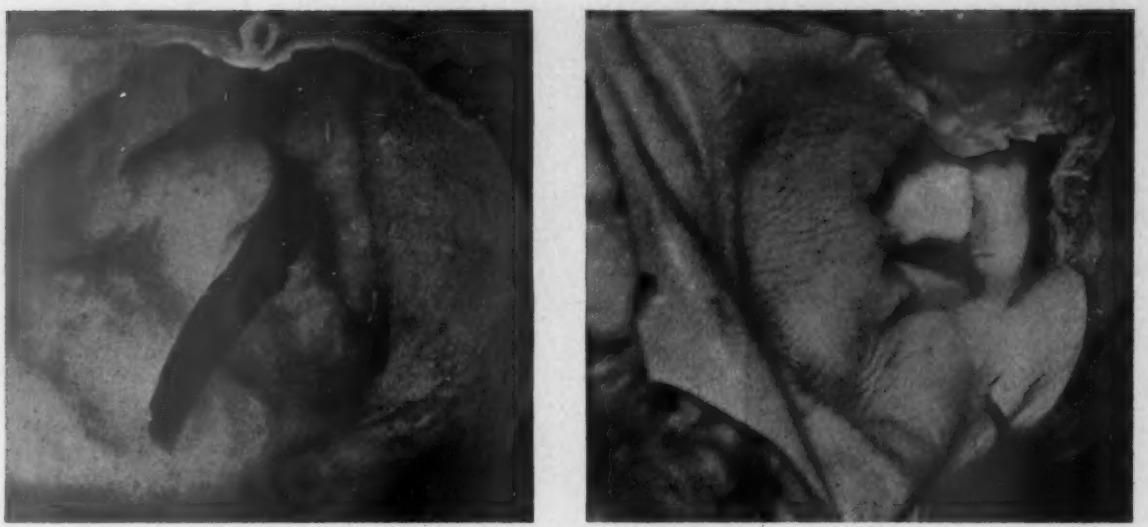


A B

FIG. 3. Case 1. A, longitudinal section of the heart showing considerable hypertrophy of the left and right ventricular myocardium. B, tricuspid orifice. The opening to the right of the small tricuspid orifice is an artifact due to a previous biopsy.

pearance of peripheral edema and ascites. In February 1954, she was hospitalized for the first time with a right-sided hydrothorax, ascites and marked edema of the lower limbs. Discharged improved, she was readmitted six weeks later presenting the same clinical picture. Unimproved by the usual therapeutic measures, the patient was transferred to the Institute. She never presented any hemotysis or bouts of acute pulmonary edema.

*On examination,* the patient could lie flat without respiratory discomfort; a pulsatile engorgement of the jugular veins was noted. The heart rate was regular at 100 beats per minute; the blood pressure, 95/78 mm. Hg. A systolic thrill and a grade 2 systolic murmur were noted over the second intercostal space, with radiation toward the left clavicle and along the left sternal border; a diastolic murmur was also heard along the left sternal border. The lungs were clear. The abdomen was distended due to the presence of ascites; the liver and spleen were palpable. The peripheral edema extended up to the knees. The venous pressure was 232 mm. of water



A B

FIG. 4. Case 1. A, mitral orifice. The absence of tissue at the lower left part of the picture is due to a biopsy. B, narrowed pulmonary orifice viewed from the opened pulmonary artery.

and the arm to tongue circulation time with Decholin® was thirty-two seconds.

*The electrocardiogram* (Fig. 1) showed sinus rhythm, atrial hypertrophy, right ventricular hypertrophy and QRS complexes of small amplitude. *On fluoroscopy and radiography* (Fig. 2A), the heart was markedly enlarged, the pulsations almost inactive and the pulmonary markings were diminished.

*The provisional diagnosis* was that of Ebstein's anomaly with pericardial effusion. *Pericardiocentesis* yielded 200 cc. of yellowish liquid. This was negative on pathologic examination. A total of 8,850 cc. of ascitic fluid was removed by three successive paracenteses. *Angiocardiography* (Fig 2B) revealed the presence of a markedly enlarged right atrium with prolongation of the opacification time.

The patient failed to respond to therapy and died with anasarca on September 11, 1954.

*Postmortem Examination:* This revealed the presence of a pericardial effusion of 400 cc. and a

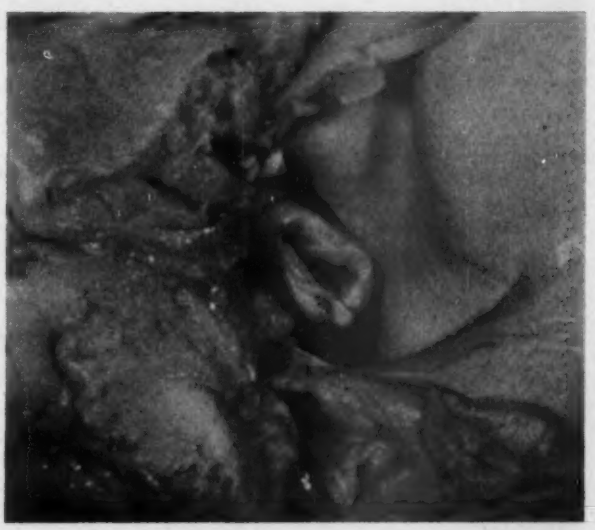


FIG. 5. Case 1. Peculiar shaped aortic orifice resembling a boat's chimney.

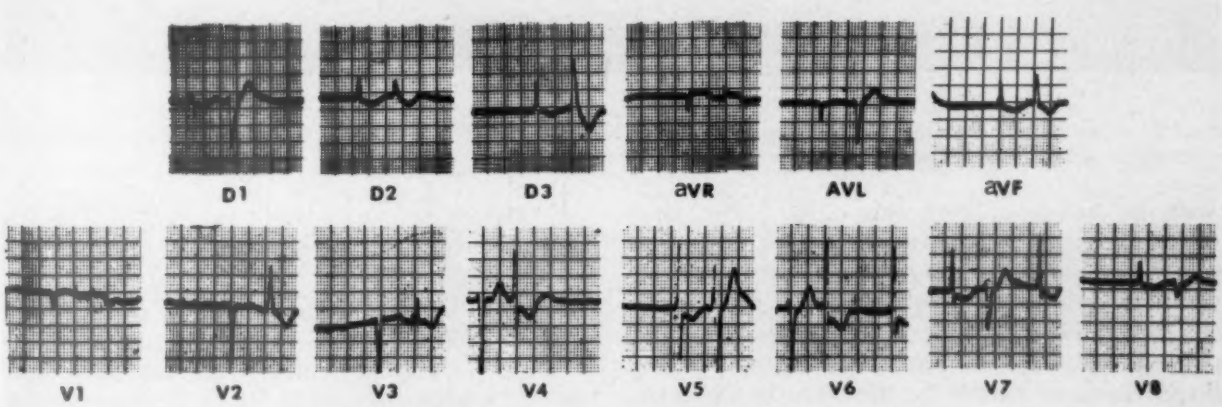
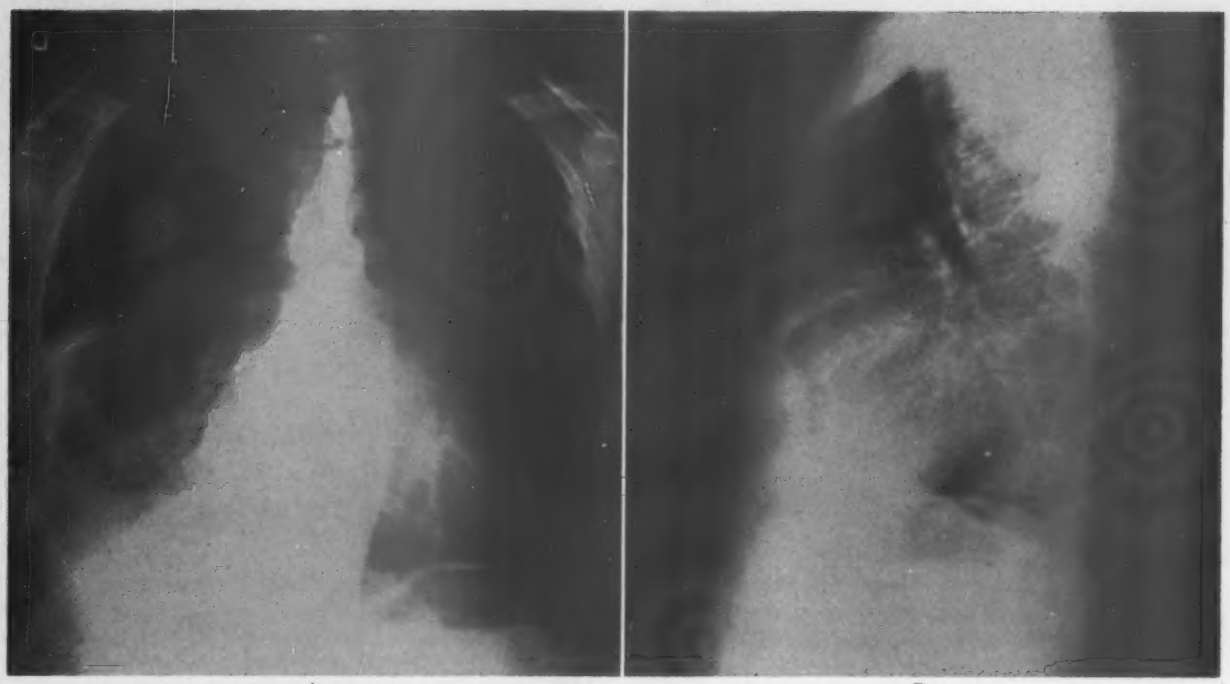
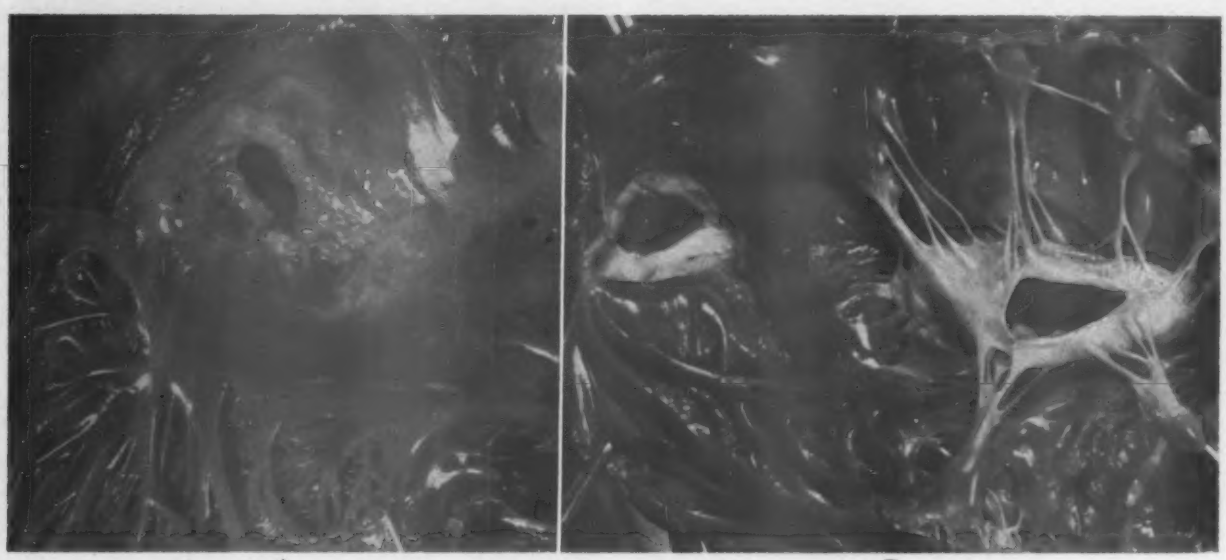



FIG. 6. Case 2. Electrocardiogram showing auricular fibrillation with bigeminy due to ventricular extrasystoles, right axis deviation and probable left ventricular hypertrophy.



A B

FIG. 7. Case 2. Teleoroentgenograms. A, posteroanterior view. B, lateral projection. There is moderate cardiomegaly, small aortic arc, straightening of the left cardiac border and right ventricular hypertrophy.

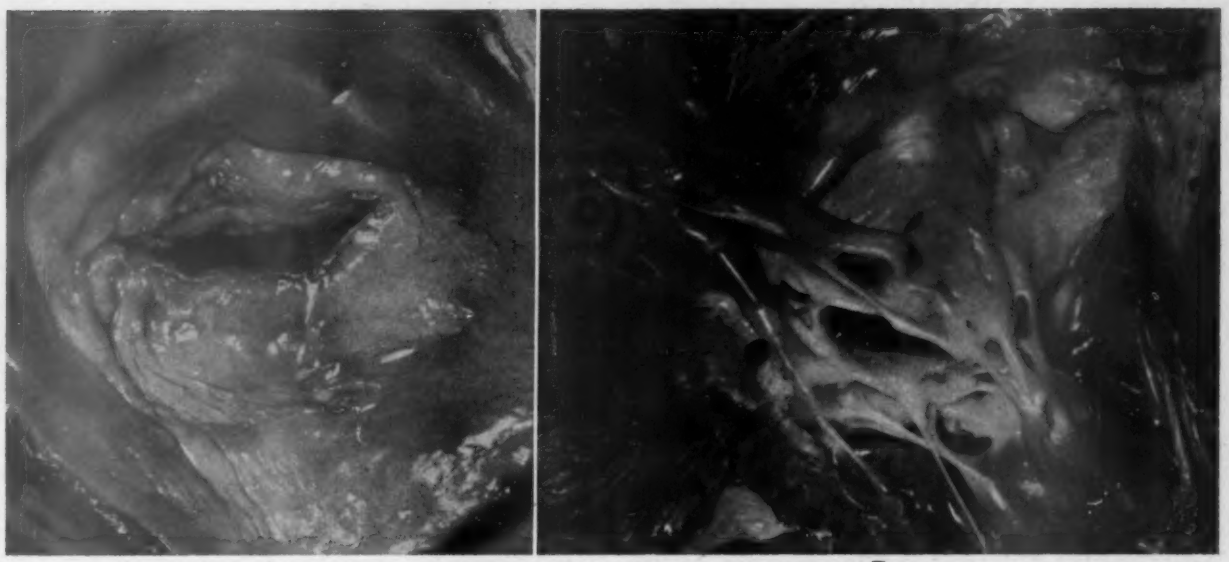


A B

FIG. 8. Case 2. A, tricuspid orifice, auricular view, showing severe stenosis. B, tricuspid valvular apparatus, ventricular view. The pulmonary orifice is seen above on the left.

markedly enlarged heart (Fig. 3A). The four valvular orifices were stenosed. The tricuspid valve measured 2.5 cm. in circumference (Fig. 3B); the mitral valve admitted the tip of the little finger (Fig. 4A). The pulmonary orifice, reduced to a few millimeters in size, was situated on top of a dome-shaped structure formed by the fusion of the three cusps (Fig. 4B). The aortic orifice, shaped like a boat's chimney, was formed by the fusion or the nonsegmentation of its semilunar leaflets (Fig. 5). The left ventricular wall measured 1.5 cm. in thickness and the right, 0.8 cm. (Fig. 3A). *Microscopic examination* revealed myocardial fibrosis and Aschoff nodules.

CASE 2. This thirty-three year old white man (S. M.) was hospitalized in March 1958 for possible surgical therapy. The patient had known about his heart ailment since fourteen years of age. He was



A B

FIG. 9. Case 2. A, mitral orifice, auricular view. B, mitral valvular apparatus, ventricular view. The aortic opening is seen above on the right.

FIG. 10. Case 2. Aortic orifice on the left; pulmonary orifice on the right.

FIG. 11. Case 2. Ventricular view of the pulmonary outflow tract showing that the stenosis is purely valvular.

unable to practice any sport soon thereafter because of progressive dyspnea on exertion. However, the patient continued his sedentary work until several months prior to his admission. Nothing in his past history could be interpreted as rheumatic fever.

*On admission*, the patient was orthopneic and had distended jugular veins. The heart rate was 50 per minute with a ventricular bigeminy; his blood pressure was 120/60 mm. Hg. A grade 2 systolic murmur, heard at the aortic area, radiated toward the neck; a grade 2 diastolic murmur was heard along the left sternal border. At the apex a loud first sound was present, in addition to a grade 2 systolic murmur that radiated toward the left axilla, and a loud diastolic murmur of mitral stenosis. The findings indicative of right-sided pleural effusion were present. The liver edge was palpable 5 fingerbreadths below the costal margin. There was no peripheral edema.

*The electrocardiogram* (Fig. 6) showed auricular fibrillation with ventricular premature beats resulting in a bigeminal rhythm, right axis deviation and probable left ventricular hypertrophy. *On fluoroscopy and x-ray examination* (Fig. 7), the heart was markedly enlarged with biventricular hypertrophy.

*The clinical diagnosis* was that of trivalvular heart disease (mitral, aortic, tricuspid) complicated by atrial fibrillation with slow ventricular response and bigeminy due to overdigitalization.

*Right heart catheterization* (Table 1) revealed a

TABLE I
Right Heart Catheterization Findings

| Area | Pressures (mm. Hg) | |
|---|---|---|
| | Case 2 | Case 3 |
| Right atrium | 20/16(20)* | 12/0(10) |
| Right ventricle | 76/10(18) | 48/6(20) |
| Pulmonary artery (trunk) | 32/18(20) | 44/14(26) |
| Right pulmonary artery | 40/15(24) | ... |
| Pulmonary wedge | ... | 20/8(10) |

* Figures in parentheses indicate the mean pressures.

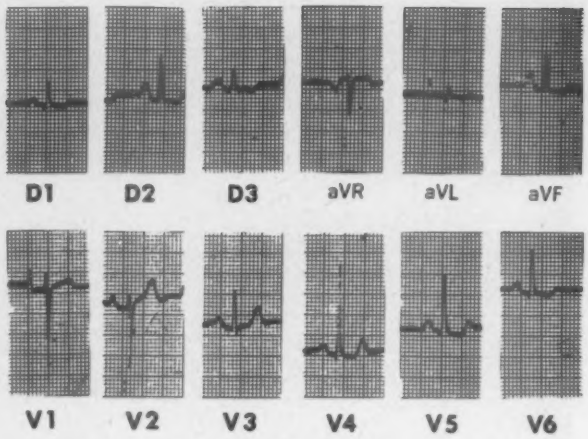
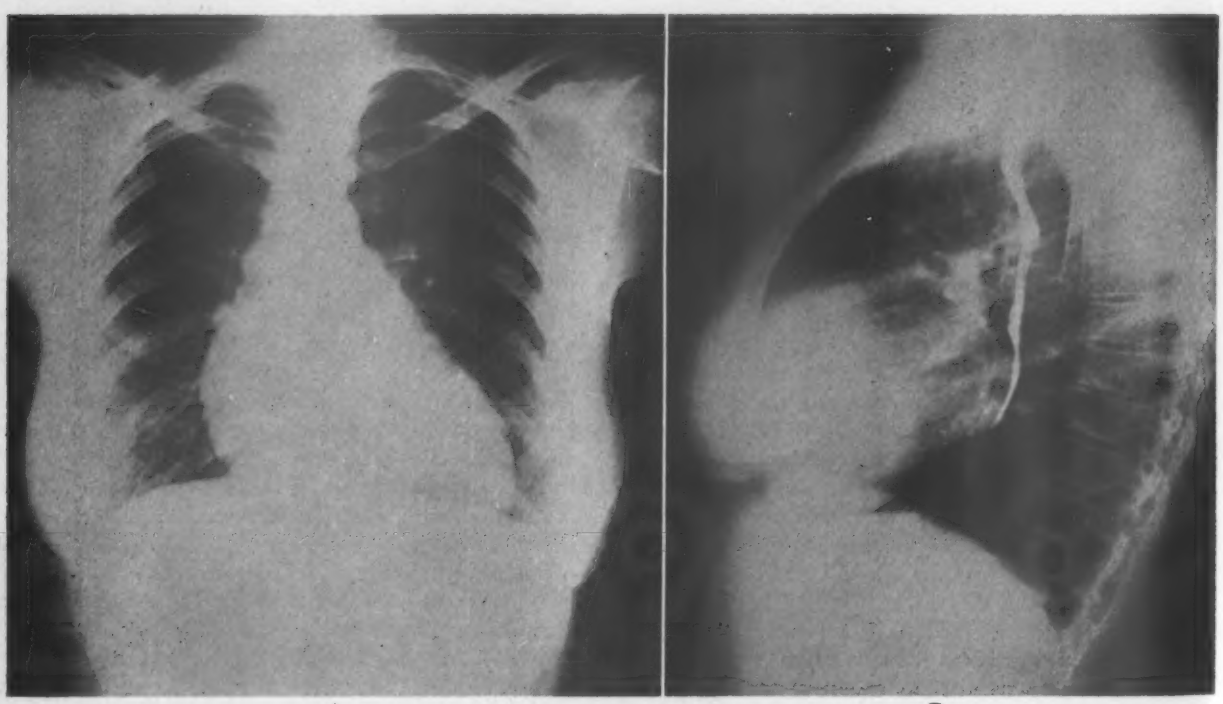



FIG. 12. Case 3. Electrocardiogram showing biauricular and left ventricular hypertrophy.

pressure of 20/16 mm. Hg in the right atrium with a mean pressure of 20 and a systolic regurgitation wave, a pressure of 76/10 mm. Hg with a mean pressure of 18 in the right ventricle, a pressure of 32/18 mm. Hg with a mean pressure of 20 in the pulmonary trunk, and 40/15 mm. Hg with a mean pressure of 24 in the right pulmonary artery. The pulmonary wedge pressure tracing was unsatisfactory. The brachial artery pressure curve showed an anacrotic notch with a significant delay in total ejection time. The clinical diagnosis of trivalvular heart disease was thus confirmed and pulmonary valve stenosis was also added.

With digitalis and diuretic therapy, the signs and symptoms of cardiac failure regressed but the bigeminal rhythm persisted in spite of procaine amide therapy. One day, when quinidine was substituted for procaine amide, the patient died suddenly while reading. He had received only three 0.2 gm. doses of quinidine the day prior to his death.

*Postmortem Examination:* The heart weighed 550 gm. and the four valvular orifices were stenosed. The tricuspid orifice (Fig. 8A) measured 1.8 cm. by 0.6 cm., the leaflets were thickened, fibrosed and welded together and then unidentifiable. The mitral orifice measured 2 cm. by 0.8 cm. (Fig. 9), the pulmonary, 1.8 cm. in diameter and the aortic



A B

FIG. 13. Case 3. Teleroentgenograms in posteroanterior (A) and lateral (B) projections, showing enlarged heart with mitral silhouette, right ventricular hypertrophy and enlargement of the left atrium.

FIG. 14. Case 3. Aortic orifice after surgical opening.

less than 2 cm. The pulmonary and aortic semilunar valves were thickened, fibrosed, their margins forming a ridge of 3 to 4 mm. in thickness (Figs. 10, 11). Two calcified areas were found on the ventricular surface of one of the semilunar aortic leaflets. The left ventricular wall measured 1.5 cm. in thickness and the right ventricle, 0.6 cm.

*On microscopic examination*, irregular zones of fibrosis, periarterial concentric fibrosis and typical Aschoff nodules were found.

CASE 3. L. S., a forty-three year old white woman referred for cardiac surgery, was first examined in May 1956, at age forty-two. She suffered from acute rheumatic fever at age seven and was spared all physical exertion, including climbing stairs, up to the age of eighteen. Progressive dyspnea on exertion appeared with her first job at age eighteen. Her single pregnancy at age twenty-seven years was uneventful. At age forty-one she began to have retrosternal pain on exertion, possibly anginal in origin; at age forty-two she was unable to climb at all and her physical activities were considerably limited due to exertional dyspnea and easy fatigability.

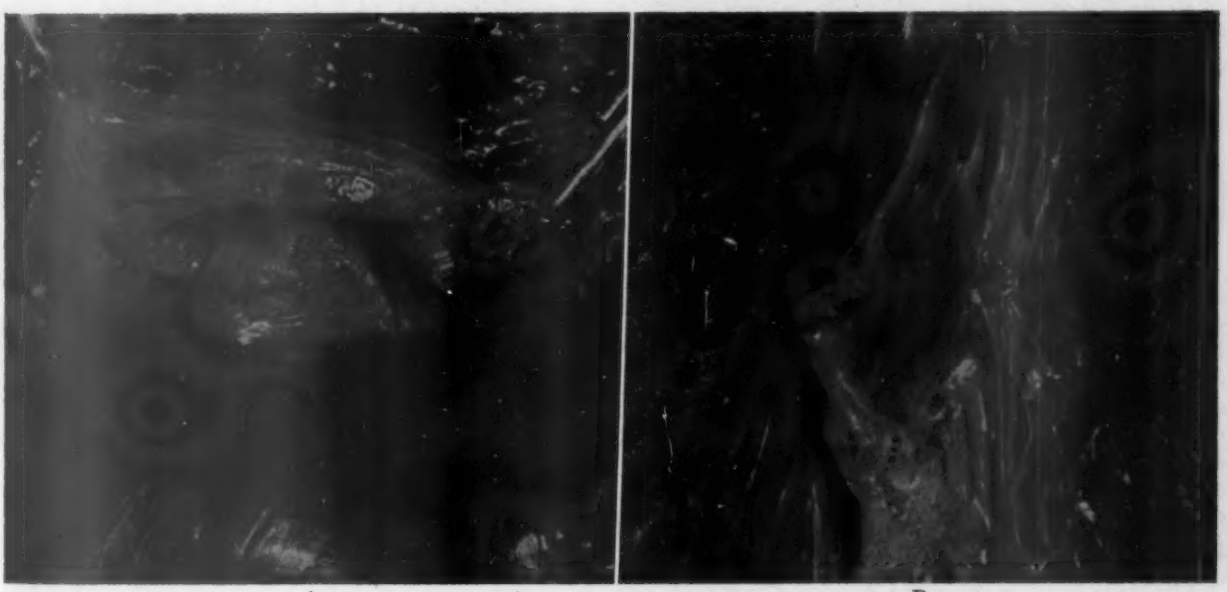
*On examination*, the heart rate was regular at 64 per minute, the blood pressure 136/80 mm. Hg. The typical auscultatory findings of mitral stenosis were heard at the apex in addition to a grade 2 systolic murmur radiating to the axilla. At the base of the heart, along the left sternal border and at the tricuspid area, a grade 2 systolic murmur was heard. A mild diastolic murmur was also heard in the aortic area. The lungs were clear and no peripheral edema was present.

*The electrocardiogram* (Fig. 12) showed evidence of biauricular and left ventricular hypertrophy. *On fluoroscopy and roentgenography* (Fig. 13) there was moderate cardiomegaly, biventricular hypertrophy and an enlarged left atrium.

*Right heart catheterization* (Table 1) revealed a right atrial pressure of 12/0 mm. Hg with a mean pressure of 10, a right ventricular pressure of 48/6 mm. Hg with a mean pressure of 20, and a pulmonary artery pressure of 44/14 mm. Hg with a mean pressure of 26. It should be noted that no systolic gradient existed across the pulmonary valve. The pulmonary wedge pressure was 20/8 mm. Hg with a mean pressure of 10 which rose to 34 mm. at mild exertion.

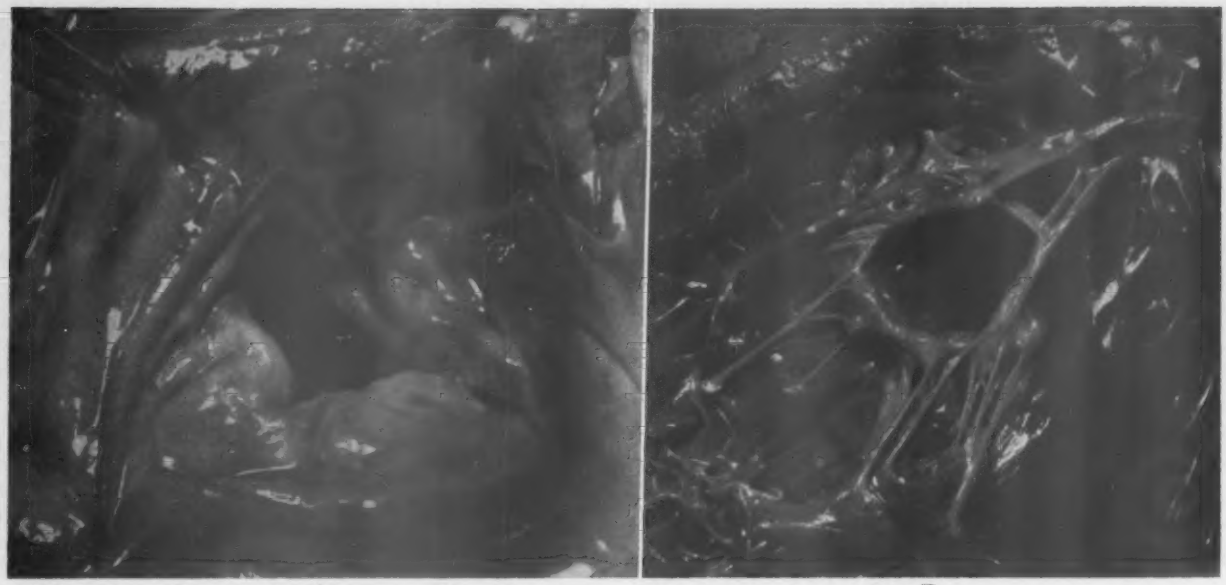
The patient was referred for cardiac surgery for a double commissurotomy, mitral and aortic. She died from ventricular fibrillation during surgery on the mitral valve after an adequate aortic commissurotomy had been performed.

*Postmortem Examination:* The heart weighed 500



A B

FIG. 15. Case 3. A, mitral orifice, auricular view. B, mitral valvular apparatus, ventricular view.



A B

FIG. 16. Case 3. A, tricuspid orifice, auricular view. B, tricuspid valvular apparatus, ventricular view.

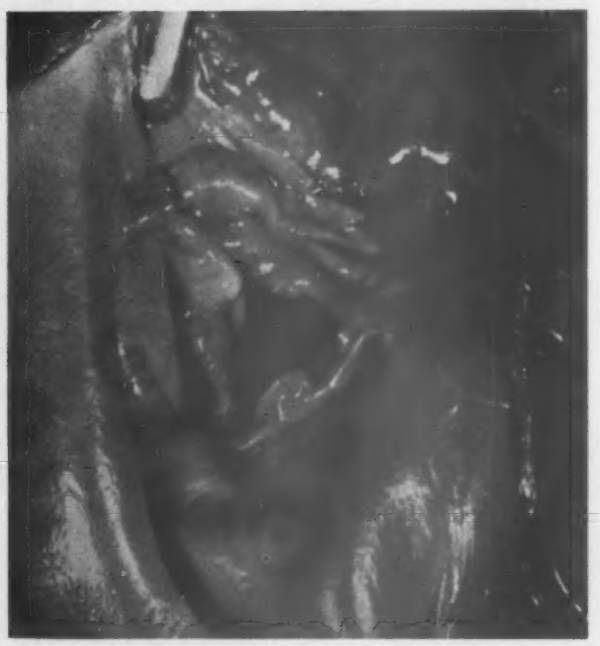


FIG. 17. Case 3. Pulmonary orifice.

gm. The four valvular orifices were involved by a fibrotic process, the various orifices narrowed to a different degree. The aortic valve, reported by the surgeon to be the size of a match head, had been opened to 2.5 cm. in diameter (Fig. 14). Two of the commissures had been fractured almost to their entire length. The valvular leaflets were thick and fibrosed. The mitral opening (Fig. 15) measured 2 mm. in its widest diameter, and its margins consisted of a fibrous ridge that gave to the exploring finger the resistance of a sphincter. The tricuspid orifice (Fig. 16) was markedly narrowed and measured 2.2 cm. in diameter. The pulmonary valve (Fig. 17) had a diameter of 1.9 cm.; its leaflets were thickened, particularly at the margins, giving a vegetation-like appearance. The right ventricular wall measured 6 mm. in thickness and the left, 1.5 cm.

*Microscopic examination* revealed a moderate degree of coronary atherosclerosis, focal myocardial and perivascular fibrosis and a small number of Aschoff nodules.

## COMMENTS

Rheumatic involvement of the pulmonary valve, particularly with functional impairment, is indeed rare. During the past six years, three cases of panvalvular lesions, presumably of rheumatic origin, have been observed at the Montreal Institute of Cardiology. The first case was diagnosed at autopsy. The second patient, in whom the diagnosis of mitral, aortic and tricuspid stenosis had been made on a clinical basis, was found to have a pulmonary stenosis as well at cardiac catheterization. The third patient, in whom no ventricular pulmonary gradient had been noted at catheterization, was operated for combined mitral and aortic stenosis. The postmortem examination revealed extensive rheumatic involvement of the pulmonary valve but only slight stenosis.

These quadrivalvular stenotic lesions do not produce a constant and definite clinical picture, the various symptoms and signs being related to the relative importance of each stenosis. The auscultatory findings, as in an isolated lesion, thus depend upon the various

valvular flows. Radiologic and electrocardiographic evidence of right heart involvement is predominant since mitral and pulmonary lesions both produce an added strain on the right ventricle. Left ventricular strain becomes evident only in the presence of an adequate cardiac output. Episodes of acute left heart failure were not present in these patients, the left ventricle most likely being protected by the diminished pulmonary blood flow resulting from the right-sided valve stenosis. Fatigue and dyspnea were the only symptoms of left heart failure.

The clinical course of the disease is that of a satisfactory state of relative compensation of more or less long duration, followed by a rapid deterioration after signs and symptoms of right heart failure appear. Digitalis and diuretic therapy do not usually prevent recurrent bouts of cardiac failure. Surgical correction is believed feasible with the aid of extracorporeal circulation.


## Summary

Three cases of quadrivalvular rheumatic lesions are reported, all proved by autopsy examination. The symptomatology of these quadrivalvular lesions varies according to the relative stenotic involvement of each valve. The clinical course rapidly deteriorates once right-sided heart failure appears. Surgical correction with the aid of extracorporeal circulation is feasible in the earlier stage of the disease.



## Acknowledgment

We wish to express thanks to Dr. Y. Desrochers who kindly permitted us to use the data concerning the second case of this report.


## References


1. Chavez, I., Ponce de Leon, J., Robles and Gil, J. Las valvulopathias reumaticas en 1000 casos. *Arch. Inst. cardiol. México*, 28: 492, 1958.
2. Herrmann, G. R. Chronic cardiac valvular disease. In: Oxford Medicine, vol. 2, part 2, p. 492. Edited by Christian, H. A. and MacKenzie, J. New York, 1944. Oxford University Press.
3. Coupland, S. *Tr. Path. Soc. London*, 26: 22, 1875.
4. Newton Pitt, M. Quoted in reference 6.
5. McGuire, J. and McNamara, R. J. Organic and relative insufficiency of the pulmonary valve. *Am. Heart J.*, 14, 562, 1937.
6. Evans, P. R. C. Rheumatic involvement of all four heart valves. *Guy's Hosp. Rep.*, 102: 146, 1953.

# Adams-Stokes Attacks Precipitated by Swallowing in a Patient with Bronchial Carcinoma*

BENGT W. JOHANSSON, M.D.

Malmö, Sweden

ADAMS-STOKES SYNDROME has been defined in various ways by different authors.[1] Taking into consideration both clinical and historic facts, the best definition should be as follows: acute cerebral ischemia in non-anesthetized patients on the basis of a change in cardiac rhythm. Multiple attacks, often serious with long periods of unconsciousness, are also characteristic for the syndrome. The cerebral ischemia can cause symptoms from the slightest dizziness or faintness to deep unconsciousness with or without convulsions. The arrhythmias vary. Complete heart block during the free periods is common, but not necessary for the diagnosis.

The causes of Adams-Stokes attacks are many; they have been divided into cardiac and neurogenic. Before the detection of the conduction system in the heart cerebral lesions were commonly considered the basis of Adams-Stokes attacks.

In 1793 Spens[2] described the case of a patient with convulsions coming at different intervals; during the attack hardly any pulse could be felt for many seconds. The attacks seemed to be precipitated by food. Volhard[3] discussed whether vagus stimulation can cause cardiac arrest and loss of consciousness. He thought that two cases reported earlier were in favor of this; namely, a case reported by Neubürger and Edinger[4] with a varicose change in the medulla oblongata and a case described by Zur Helles[5] in which bradycardia and unconsciousness developed during an inflammation of the vagus nerve causing a palsy of the recurrent nerve. In this connection it is interesting to note that the cardiac asystole produced in dogs with vagal stimulation increased in duration when the animals were rendered acidotic by breathing a gas mixture containing 20 per cent carbon dioxide.[6] v. Hoesslin and Klapp[7] in 1924 reported the case of a twenty-eight year old woman who had frequent Adams-Stokes attacks after a tonsillectomy. The attacks disappeared after vagotomy was performed. Gerhard[8] and Gluch[9] each described a patient with Adams-Stokes attacks which they ascribed to the vagus nerve being infiltrated with a malignant tumor. In Reuling's[10] case a bronchogenic sarcoma had metastasized to the heart and destroyed the bundle of His. Touching a certain part of the larynx caused pains and Adams-Stokes attacks in a patient described by Flaum and Klima.[11] The patient was cured some time after an injection of alcohol into the pertinent part of the larynx. Medvei and Uiberall[12] described a similar case occurring after tonsillitis. In Reiniger's[13] case, anesthesia of the larynx (and only of the piriform sinus) stopped the attacks.

Weiss and Ferris[14] reported Adams-Stokes attacks precipitated by food, especially sticky foods such as peanut butter and crackers, in a patient with a traction diverticulum in the esophagus. James'[15] and Correll and Lindert's[16] patients also had a diverticulum in the esophagus. Starling's[17] patient could produce attacks voluntarily by repeated swallowing. In three cases described by Brandenburger,[18] attacks of unconsciousness were precipitated by certain movements of the head. The author claimed that tumors in the neck pressed on the carotid sinus with movements of the head. In one case the tumors consisted of fat pads; these patients were very fat and the attacks disappeared after their weight was reduced.

* From the Cardiological Laboratory, Department of Medicine, Allmänna Sjukhuset, Malmö, Sweden.

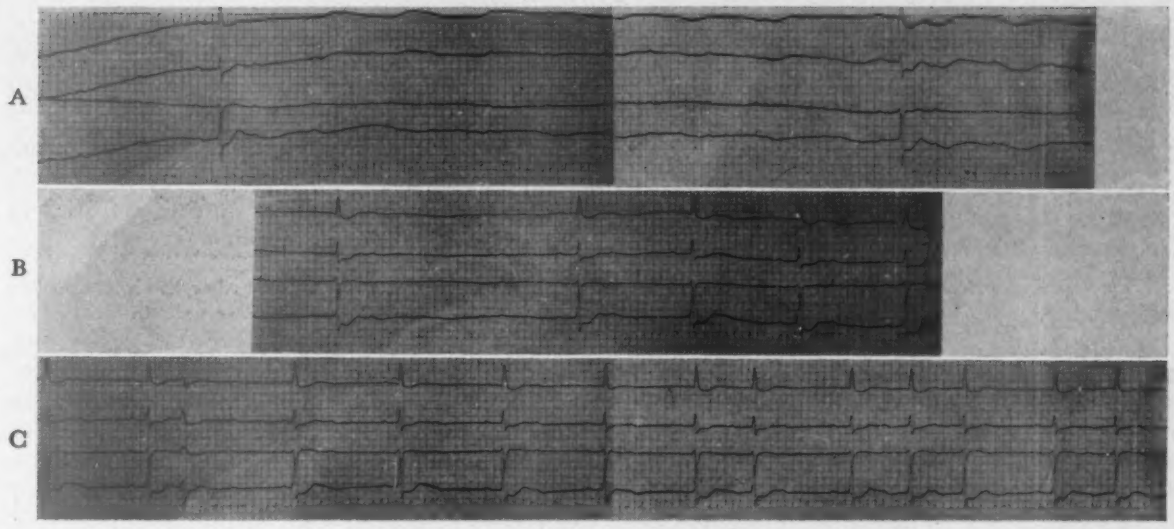



FIG. 1. Electrocardiogram after swallowing a tablet of prochlorperazine. A, just after swallowing tablet; B, one minute after swallowing; C, two minutes after swallowing. The four leads recorded simultaneously are the three standard leads and lead $V_4$. The distance between heavy vertical lines is 0.10 second.

Scott and Sancetta[19] could produce attacks of cerebral ischemia caused by ventricular fibrillation in a patient by introducing a finger into the anus. In a patient described by Cookson,[20] raising of the left arm (but not the right) and pressure on the left carotid sinus caused ventricular arrest, only if normal rhythm existed before the "experiment." Bockel[21] has reported a strange case of a patient who had Adams-Stokes attacks in connection with exercise and certain movements of the body. Furthermore, on one occasion, a singultus appeared at the same rate as the heart beats. It was possible to count the heart rate by counting the singultus. A vagal reflex was considered the causal mechanism also in the cases reported by Laslett,[22] Wedd et al.[23] and Trocmé.[24] Kjellin et al.[25] described a case and reviewed the literature on glossopharyngeal neuralgia associated with cardiac arrest.

Some authors[7,26] claim that atropine is the drug of choice in differentiating between the cardiac and the neurogenic form of Adams-Stokes attacks. The attacks are said to disappear after administration of atropine if they are of neurogenic origin.

The following is the report of a patient with an adenocarcinoma of the left lung metastasizing to different parts of the body; she had repeated attacks of partial loss of consciousness often precipitated by swallowing solid food.

## CASE REPORT

The patient was a seventy-four year old woman. She had felt well until the last year when she began to complain of pain in her hips, dyspnea and nervousness. One month before hospitalization she fainted in her bathroom. The same thing happened the next day. These attacks of unconsciousness were very short and when the doctor arrived she already felt well again. A more severe attack of the same type occurred on the day of hospitalization.

*Physical examination* revealed an elderly woman with slight edema of the legs. The heart was enlarged; this was later confirmed by x-ray examination. The pulse was 76 beats per minute, blood pressure 170/90 mm. Hg. There was a grade 3 systolic murmur over the entire precordium. Over the lower part of the left lung the percussion tone was dull and respiratory sounds were decreased.

*Clinical Course:* After digitalization her condition was improved for a short time but symptoms developed again. X-ray films showed a left-sided pleural effusion. The microscopic diagnosis of a bluish tumor that was extirpated from the abdominal wall was skin metastasis from an adenocarcinoma. The pathologist was unable to state the origin of the adenocarcinoma. Two weeks after hospitalization the patient became unconscious after swallowing a half-solid bit of food. On the same occasion she also had a few convulsions, became somewhat cyanotic and perspired. The pulse was slower than before the attack (48 per minute). The next day she had another "heart attack," the pulse was slow and an electrocardiogram recorded a few minutes afterward showed 2 : 1 A-V block.

The same day as the occurrence of the second attack in the hospital the patient was taken to the cardiological laboratory where she was given a small tablet of prochlorperazine.* In connection with the swallowing of this tablet the electrocardiogram showed

* These tablets are about the same size as those of lanatoside C (Cedilanid®).

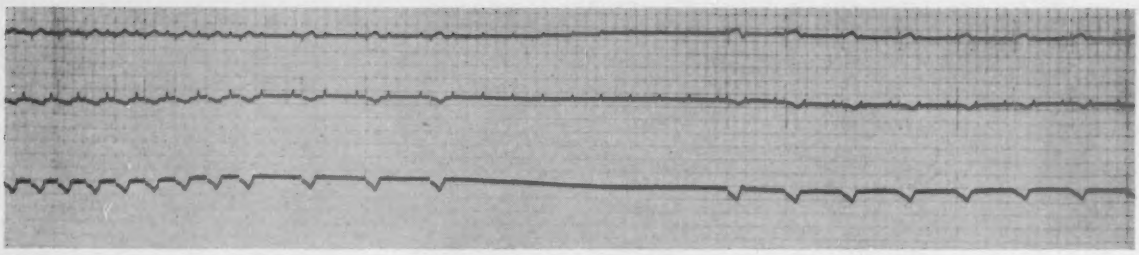


FIG. 2. Electrocardiographic registration from an isolated perfused heart of a guinea pig just after the injection into the perfusion fluid of 0.1 μg. acetylcholine. Note the persistence of P waves in the absence of ventricular complexes.

a disappearance of the ventricular activity for about nine seconds (Fig. 1). The P waves, however, persisted during this whole period. At the end of this period she became pale and semiconscious. Afterward she was not aware of what had happened during this period. The pulse rate gradually increased and after one minute there appeared a regular 2 : 1 A-V block and a ventricular rate of 40 per minute. A few minutes later a first degree A-V block began with a P-R interval of 0.32 second, sometimes interrupted by a 2 : 1 A-V block. She was then given two mouthfuls of lidocaine (Xylocain®). Swallowing this produced a new ventricular arrest, this time lasting eleven seconds. The atrial activity persisted. On both these occasions the atrial rate did not increase either before or during the ventricular asystole but decreased slightly. When her mouth and throat were well anesthetized she was again given a tablet of prochlorperazine. At the first, unsuccessful, attempt to swallow this tablet the first degree A-V block was interrupted by two beats with a 2 : 1 A-V block; this, however, happened spontaneously now and then. At the second attempt, which was successful with the aid of a little water, no rhythm changes appeared.

The outer part of the external auditory canal, that part which is innervated by the vagal nerve, was firmly rubbed. This, however, had no effect on her heart action. During the sixteen days remaining till her death the cardiac rhythm alternated often between first degree block and 2 : 1 A-V block. She had repeated Adams-Stokes attacks most often in connection with swallowing, which became so unpleasant to her that she could only take fluids or small amounts of semisolid food.

Ephedrine was given in a dose of 25 mg. three times daily and atropine in a dose of 0.25 mg. three times a day. Neither drug seemed to have any effect on the number of attacks.

*Postmortem Examination:* Autopsy revealed an adenocarcinoma in the upper lobe of the left lung with metastases in regional lymph nodes, lungs, epicardium, liver, spine, suprarenals, left kidney and skin. There were also signs of a left-sided hypertrophy of the heart and cardiac decompensation. A small diverticulum (1 by 1 by 3 mm.) was found in the esophagus.

*Microscopic examination* of multiple slices from lymph nodes in connection with the left vagus nerve revealed malignant infiltration in the lymph nodes closely surrounding the vagal nerve. Nowhere was tumor tissue found inside the nerve itself. Besides the metastatic infiltration on the surface of the heart there were no signs of tumor tissue in the myocardium which was almost normal with only a few fibrous areas. The conduction system was within normal limits on macroscopic examination.

## COMMENTS

The exact mechanism of precipitation of the Adams-Stokes attacks in this patient is uncertain. Brandenburger[18] is of the opinion that there was a constant pressure on the vagal nerve in his patients producing a chronic irritation. Because of this, slight pressure on the carotid sinus was enough to produce cardiac arrest. In the present case there was probably also a chronic irritation of the left vagus nerve caused by the enlarged metastatic lymph nodes. One might imagine that swallowing produced tension in the tissues surrounding the vagus nerve because of the malignant infiltration in this area. In this way a maximal stimulation of the nerve might be induced. It is, however, not likely that direct stimulation of the vagus is enough to give cardiac arrest. Weiss and Baker[27] conclude, partly on the basis of experiments performed by Iacobovici et al.,[28] that slowing of the cardiac rate via the vagus nerve is produced by reflex rather than by direct stimulation.

Also, in the present case it is likely that the ventricular arrest and accompanying Adams-Stokes attacks were released through a reflex because the symptoms disappeared if the mouth and throat were anesthetized. The exact trigger point is unknown. The patient's condition prohibited a detailed stimulation of the different parts of the upper portion of the digestive tract. The small diverticulum in the esophagus is a possible trigger point but, as noted in the review of the literature, there are other possibilities.

The concept that the attacks of ventricular arrest were of vagal origin is supported by the electrocardiogram. During the attacks a ventricular asystole appeared, the atria still beating, continuing into a 2 : 1 A-V block and later an A-V block of the first degree. This pattern of arrhythmia corresponds to the one obtained when administering acetylcholine to the isolated perfused heart of the guinea pig[29] (Fig. 2).

There has been much discussion in the literature concerning the existence of the so-called neurogenic form of Adams-Stokes syndrome. Before the conduction system was known to exist, most of the reports ascribed the attacks to cerebral factors.[1] This explanation has become less common and some authors have even denied it, citing the fact that there is often tachycardia just before the so-called neurogenic Adams-Stokes attack, which is not in agreement with a vagal influence. In the present case, however, the electrocardiogram was recorded also before the induced attack and neither before nor during the attack was there an increased heart rate. The P wave rate did not increase during ventricular arrest; there was, instead, a slight decrease.

## Summary

A case of Adams-Stokes attacks precipitated by swallowing is reported. The patient, a seventy-four year old woman, died from a carcinoma of the lung with metastases to different organs including lymph nodes surrounding the left vagus nerve.

Adams-Stokes attacks were precipitated by swallowing, especially of solid food. During the attacks, two of which were recorded electrocardiographically, there appeared ventricular arrest for nine to eleven seconds. The atria continued to beat regularly.

The mechanism for producing these attacks is discussed. It was probably a vagal reflex, the afferent stimulus originating somewhere in the upper part of the digestive tract, possibly in a very small diverticulum in the esophagus.

## References

1. Johansson, B. W. Adams-Stokes syndrome. *Am. J. Cardiol.* In press.
2. Spens, T. Medical observations. I. History of a case in which there took place a remarkable slowness of the pulse. Communicated to Dr. Duncan, by Dr. Thomas Spens, physician in Edinburgh. In: Med. Commentaries, vol. 7, p. 463. Edinburgh, 1793.
3. Volhard, F. Uber die Beziehungen des Adams-Stokesschen Symptomenkomplexes zum Herzblock. *Deutsches Arch. klin. Med.*, 97: 348, 1909.
4. Neubürger and Edinger, quoted from reference 3.
5. Zur Helles, quoted from reference 9.
6. Young, W. G., Jr., Sealy, W. C., Harris, J. and Botwin, A. The effects of hypercapnia and hypoxia on the response of the heart to vagal stimulation. *Surg. Gynec. & Obst.*, 93: 51, 1951.
7. v. Hoesslin, H. and Klapp, R. Vagusresektion bei Adams-Stokes'schen Symptomenkomplex. *Klin. Wchnschr.*, 3: 1211, 1924.
8. Gerhard, quoted from reference 9.
9. Gluch, B. Electrocardiographische Beobachtungen bei dem Morgagni-Adams-Stokes'schen Symptomen-Komplex. *Ztschr. Kreislaufforsch.*, 24: 561, 1932.
10. Reuling, J. R. and Razinsky, L. Metastatic bronchiogenic carcinoma of the heart. *Am. Heart J.*, 21: 470, 1941.
11. Flaum, E. and Klima, R. Ein neurogen ausgelöster Fall von Adams-Stokes. *Klin. Wchnschr.*, 11: 1192, 1932.
12. Medvei, C. V. and Uiberall, H. Ueber schwere, von der Mund- und Pharynxschleimhaut auslösbare Rhythmusstörungen des Herzens. *Wien. klin. Wchnschr.*, 51: 234, 1938.
13. Reiniger, A. Die Rolle der Sensibilitätsstörungen im Kehlkopf bei der Entstehung des Adams-Stokes'schen Symptomenkomplexes. *Ztschr. Hals-Nasen- u. Ohrenh.*, 31: 531, 1932.
14. Weiss, S. and Ferris, E. B., Jr. Adams-Stokes syndrome with transient complete heart block of vagovagal reflex origin. *Arch. Int. Med.*, 54: 931, 1934.
15. James, A. H. Cardiac syncope after swallowing. *Lancet*, 1: 771, 1958.
16. Correll, H. L. and Lindert, M. C. F. Vagovagal syncope: report of a case apparently induced by digitalization. *Am. Heart J.*, 37: 446, 1949.
17. Starling, H. J. Heart block influenced by the vagus. *Heart*, 8: 31, 1921.
18. Brandenburger, P. Über eine besondere Ursache Adams-Stokes'schen Anfälle. *Ztschr. Kreislaufforsch.*, 30: 246, 1938.
19. Scott, R. W. and Sangetta, S. M. Stokes-Adams attacks induced by rectal stimulation in a patient with complete heart block. *Circulation*, 2: 886, 1950.
20. Cookson, H. Paroxysmal ventricular standstill. *Brit. Heart J.*, 14: 350, 1952.
21. Bockel, P. Morgagni-Adams-Stokes-Symptomenkomplex bei Herzblock mit abnorm langsamer Frequenz. *Ärztl. Wchnschr.*, 9: 785, 1954.
22. Laslett, E. E. Syncopal attacks associated with prolonged arrest of the whole heart. *Quart J. Med.*, 2: 347, 1908.
23. Wedd, A. M., Springs, C. and Wilson, D. C. Standstill of the heart of vagal origin. *Am. Heart J.*, 5: 493, 1930.
24. Trocmé, P. Étude des accidents syncopaux au cours des arythmies. Paris, 1927. Quoted in reference 23.
25. Kjellin, K., Müller, R. and Widén, L. Glossopharyngeal neuralgia associated with cardiac arrest and hypersecretion from the ipsilateral parotid gland. *Neurology*, 9: 527, 1959.

26. Nagayo, M. Pathologisch-anatomische Beiträge zum Adams-Stokes'schen Symptomenkomplex. *Ztschr. klin. Med.*, 67: 495, 1909.
27. Weiss, S. and Baker, J. P. The carotid sinus reflex in health and disease. *Medicine*, 12: 297, 1933.
28. Iacobovici, I., Nitzescu I. I. and Pop, A. Experimentelle Untersuchungen über die Physiologie der Carotisdrüse beim Menschen. *Ztschr. ges. exper. Med.*, 66: 359, 1929.
29. Johansson, B. and Vendsalu, A. The influence of adrenaline, noradrenaline, and acetylcholine on the electrocardiogram of the isolated perfused guinea-pig heart. *Acta physiol. Scandinav.*, 39: 356, 1957.

# Intracardiac Amputation of a Plastic Catheter during Left Heart Catheterization*

TSUNG O. CHENG, M.D.

Brooklyn, New York

MANY METHODS of left heart catheterization have been introduced during the last ten years.[1-7] There are advantages and disadvantages to each of these methods. Both major and minor complications have been reported by various investigators who have an abundance of experience in using any one of these technics. Fortunately, in the majority of the cases the after-effects are usually inconsequential. Death is rare.

The usual procedure in catheterization of the left side of the heart is to puncture the left atrium with a needle and then to introduce a fine plastic catheter through the needle down into the left ventricle. During the withdrawal of the plastic tubing through the needle a segment of the former may be caught by the sharp tip of the needle and, if withdrawal is continued, may be sheared off. However, intracardiac amputation of a plastic catheter has been reported only once[8] although many authors have warned about its possible occurrence and dire consequences. The purpose of this communication is to report another instance of this complication with its serious hemodynamic effects and eventual recovery of the catheter following surgical intervention.

## CASE REPORT

The patient, a twenty-six year old Negro woman, was first seen in the Cardiac Clinic of the Brooklyn Hospital because of extertional dyspnea of two years' duration with progressive worsening during the last six months. No history of rheumatic fever was obtained. At the age of seventeen years the patient suffered a "stroke" with transient left hemiplegia. At that time a diagnosis of rheumatic heart disease was made in another hospital. On two occasions, three years and one year before her visit to the clinic, brisk hemoptysis occurred and was associated with paroxysmal nocturnal dyspnea.

*Physical examination* revealed a blood pressure of 100/60 mm. Hg and a regular pulse of 76 per minute. The point of maximal cardiac impulse was in the fifth intercostal space in the midclavicular line. The first sound at the apex was not accentuated. There was a loud, harsh systolic murmur at the apex and also a moderately loud and long mid-diastolic rumbling murmur over the same area. The pulmonic second sound was accentuated and closely split.

An electrocardiogram revealed P mitrale but no definite evidence of enlargement of either ventricle. Fluoroscopy of the chest and roentgenograms with barium swallow demonstrated definite right ventricular and left atrial enlargement but equivocal left ventricular enlargement.

*The clinical diagnosis* was rheumatic heart disease with combined stenosis and insufficiency of the mitral valve. The predominant lesion was thought to be mitral stenosis.

*Cardiac Catheterization:* On November 3, 1959 the patient underwent a combined right and left heart catheterization. A standard right heart catheterization was first performed with the patient in the supine position. After a wedged pulmonary artery pressure was recorded, the catheter was withdrawn into the main branch of the pulmonary artery and a Fick cardiac output determination was performed. The patient was then placed in the prone position and left atrial puncture was performed through a six inch 18-gauge thin-walled needle via the posterior paravertebral approach. A four foot polyvinyl catheter was then introduced through the needle. Attempts to pass the catheter through the mitral valve were unsuccessful. At no time was any tug or resistance felt by the operator when the catheter was withdrawn. Upon withdrawal of the plastic catheter on the last occasion it was discovered that it was shorter by seventeen inches. Multiple runs of atrial and ventricular extrasystoles developed with accompanying hypotension, substernal pain and dyspnea, lasting for over two hours after the procedure. With intravenous administration of l-norepinephrine and procaine amide the arrhythmia seemed to subside greatly. However, sinus tachycardia with occasional runs of atrial extrasystoles persisted.

* From the Cardiopulmonary Laboratory, The Brooklyn Hospital and the Department of Medicine, State University of New York College of Medicine, Brooklyn, New York.

*Surgical Findings:* Eight hours later the patient underwant emergency left thoracotomy. Exploration of the left atrium revealed the presence of the missing seventeen inches of polyvinyl catheter curled up above the mitral valve ring. It was removed without difficulty. Palpation of the mitral valve revealed a marked degree of mitral stenosis and a mild degree of mitral insufficiency. The stenotic valve was adequately finger-fractured with no change in the degree of regurgitation through the mitral valve. The patient withstood the procedure well. Postoperative course was uneventful and the patient was discharged on November 20, 1959.

## Comment

Left heart catheterization is a relatively new technic used in the study of the hemodynamics of the left side of the heart. It differs from right heart catheterization principally in that in all the currently employed methods, except the retrograde technic, a needle instead of a catheter is used to enter the left side of the heart, either the left atrium or the left ventricle. To enter an adjoining heart chamber or a great vessel a fine plastic catheter is introduced through the indwelling needle. Due to the narrow lumen of the needle a radiopaque nylon-woven catheter cannot be used for such a purpose. Only fine plastic catheters can go through such a needle. The manipulation of the nonradiopaque plastic catheter within the heart is therefore an entirely blind procedure. Due to the sharpness of the needle bevel and the tight fit between the needle and the catheter, withdrawal of the catheter inside the needle may well result in scraping from the external wall of the plastic catheter, or even amputation of the catheter by the needle tip. This is more likely to occur with the polyvinyl and nylon catheters both of which are more rigid than the polyethylene catheters. *In vitro*, scraping almost inevitably resulted (more if the angulation were more acute) when either a polyvinyl or polyethylene catheter was pulled back through the needle if the catheter formed an obtuse angle with the needle at its tip. It is no surprise that the entire width of the catheter may be sheared off if angulation becomes too sharp. Angulation of the catheter with the needle tip will occur frequently inside the left atrium as long as the manipulation of the catheter within the needle is not under direct visual control.

Although the manufacturer of the plastic catheter has warned against withdrawal of this type of catheter through the needle, this is an unavoidable step during manipulation of the catheter in left heart catheterization. Although many investigators have warned against forceful pulling of the plastic catheter during withdrawal through a needle, our unfortunate experience indicates that amputation can occur without much warning to the operator. In fact, our *in vitro* experiments demonstrate that various degrees of scraping invariably occur every time the plastic catheter is being withdrawn at an angle against the needle bevel. One might wonder if some of the minor hemodynamic complications reported following left heart catheterization may not be due to embolization of these plastic "scrapings." On the other hand, if only a very short segment of the fine plastic catheter is cut off no untoward reaction may develop unless the fragment obstructs an end artery in an area which can produce symptoms.

Since the above unfortunate experience, all our needles used for left heart catheterization have been specially ground so that the heel of the bevel of the needle tip is round and smooth. Shearing has never occurred when a plastic catheter has been pulled through such specially ground needles, even at an angulation of less than ninety degrees. We believe that every needle used for catheterization of the left side of the heart should be so treated in order to avoid scraping of the side of the catheter or its amputation.

## Summary

A case of accidental intracardiac amputation of a plastic catheter during left heart catheterization is reported. Operation as well as mitral commissurotomy with removal of the catheter was followed by uneventful recovery of the patient.

The case is reported as a reminder of the possibility of its occurrence and the serious consequences. With proper smoothing of the heel of the bevel of the needle tip such a mishap should be preventable.

## References

1. Zimmerman, H. A., Scott, R. W. and Becker, N. O. Catheterization of the left side of the heart in man. *Circulation*, 1: 357, 1950.
2. Bjork, V. O., Malmstrom, G. and Uggla, L. G. Left auricular pressure measurements in man. *Ann. Surg.*, 138: 718, 1953.
3. Fisher, D. L. The use of pressure recordings obtained at transthoracic left heart catheterization in the diagnosis of valvular heart disease. *J. Thoracic Surg.*, 30: 379, 1955.

4. RADNER, S. Extended suprasternal puncture technique. *Acta med. Scandinav.*, 151: 223, 1955.
5. BROCK, R., MILSTEIN, B. B. and ROSS, D. N. Percutaneous left ventricular puncture in the assessment of aortic stenosis. *Thorax*, 11: 163, 1956.
6. MORROW, A. G., BRAUNWALD, E., HALLER, J. A., JR. and SHARP, E. H. Left heart catheterization by the transbronchial route. Technique and application in physiologic and diagnostic investigations. *Circulation*, 16: 1033, 1957.
7. ROSS, J., JR., BRAUNWALD, E. and MORROW, A. G. Transseptal left atrial puncture. New technic for the measurement of left atrial pressure in man. *Am. J. Cardiol.*, 3: 653, 1959.
8. BAGGER, M., BJORK, V. O. and MALMSTROM, G. Technique and sequelae of catheterization of the left side of the heart. *Am. Heart J.*, 53: 91, 1957.

# Diagnostic Shelf

# Acute Myocardial Infarction Early and Objectively Diagnosed through Ventricular Extrasystoles*

JULES COHEN, M.D., F.A.C.C.
New York, New York

THE ELECTROCARDIOGRAM, although limited in scope, remains the most sensitive indicator of myocardial infarction. Over 90 per cent of instances of myocardial infarction can be diagnosed with the conventional electrocardiographic technics at some time during the clinical course. There is a small group of cases in which the electrocardiographic changes are not sufficiently marked or do not occur promptly enough to be helpful in making an early diagnosis.[1] This small group remains a continuous challenge to the physician who strives for early confirmation of his diagnosis.

Recently we encountered a patient with a history suggestive of acute myocardial infarction and an initial electrocardiogram in which the extrasystoles gave the first objective clue to the infarction.

## CASE REPORT

A sixty-seven year old white woman was admitted to the hospital on January 7, 1960 because of severe retrosternal pain with radiation to the left shoulder and left arm the night before admission. She had had mild retrosternal pain on exertion for the last ten years and high blood pressure for many years.

*Examination on admission* revealed frequent premature contractions and a blood pressure of 220/120 mm. Hg. She was treated with anticoagulants, quinidine and conventional drugs for myocardial infarction. On the third day the blood pressure started to fall and gradually reached "shock" levels (associated also with the clinical picture of shock), unresponsive to intravenous infusion of vasopressor drugs. She died on the fifth hospital day.

*Electrocardiograms:* The first electrocardiogram taken in the emergency room (Fig. 1) revealed normal sinus rhythm with numerous multiform ventricular extrasystoles. The normal sinus beats were nonrevealing while the extrasystoles in some precordial leads were strongly suggestive of myocardial infarction; the extrasystoles in lead $V_2$ with prominent Q waves and inverted T waves were suggestive of myocardial infarction of undetermined age. The two extrasystoles in lead $V_3$, even though they are polymorph, both reveal the pattern of acute myocardial infarction with prominent Q waves, elevation of the S-T segment and either inverted or terminally inverted T waves. The same applies to the first and last extrasystoles in lead $V_4$. An electrocardiogram taken about five hours later and on the third day (Fig. 2) revealed the acute infarction pattern also in the complexes of the basic (sinus) rhythm.

*Autopsy* confirmed the acute myocardial infarction which involved the anterior and lateral walls of the hypertrophied left ventricle. The anterior descending branch of the left coronary artery was completely occluded with a fresh thrombus.

## COMMENTS

Extrasystoles occur frequently in myocardial infarction and seem to originate in the area of reactive inflammation surrounding the infarction;[2,3] usually the diagnosis of infarction is made from the basic rhythm. However, the extrasystoles occasionally may reveal signs of infarction while the sinus beats are not characteristic or they may show typical changes earlier than the beats of the basic rhythm. Electrocardiographic signs of cardiac infarction are often obscured by intraventricular block of

* From The Department of Medicine and Cardiology, Grand Central Hospital, New York, New York.

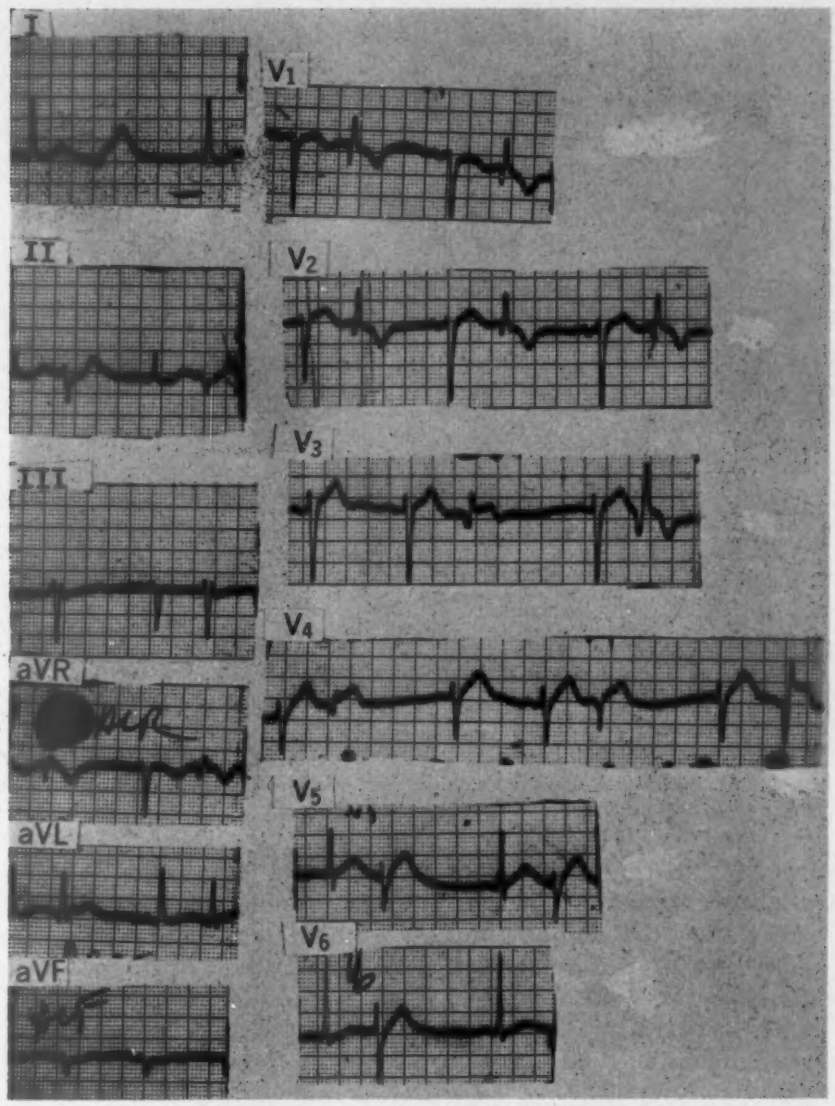



FIG. 1. The electrocardiogram on January 7, 1960 reveals numerous polymorph ventricular extrasystoles. The complexes of the basic rhythm are not diagnostic, while the ventricular extrasystoles in leads $V_2$, $V_3$ and $V_4$ are suggestive of anteroseptal wall infarction.

high degree, especially by left bundle branch block. Convincing evidence that the left bundle branch block may suppress the signs of infarction was obtained in cases in which the block was transient or intermittent.[4]

Cases in which the extrasystoles furnished the first or only clue for the diagnosis of myocardial infarction have been reported in the literature but only rarely. Electrocardiographic evidence of cardiac infarction obscured by the presence of left bundle branch block may be unmasked when a premature ventricular contraction originating on the blocked side allows both ventricles to contract reciprocally.[4,5] Wilson and Herrmann[6] were able to demonstrate the presence of an infarct in the experimental animal by this means and explained the physiologic mechanism. Dressler[5] reported a case with left bundle branch block which masked the presence of myocardial infarction; the correct diagnosis was made from two ventricular extrasystoles in lead III and confirmed at autopsy. Dressler offered two explanations as follows:

1. Occasionally, ventricular premature contractions may originate from a focus so located that the excitation wave activates the two ventricles which, in the presence of intraventricular block, are activated one after another in approximately normal sequence; then the premature beats resemble normal complexes. This may happen even when the regular beats display features of bundle branch block.

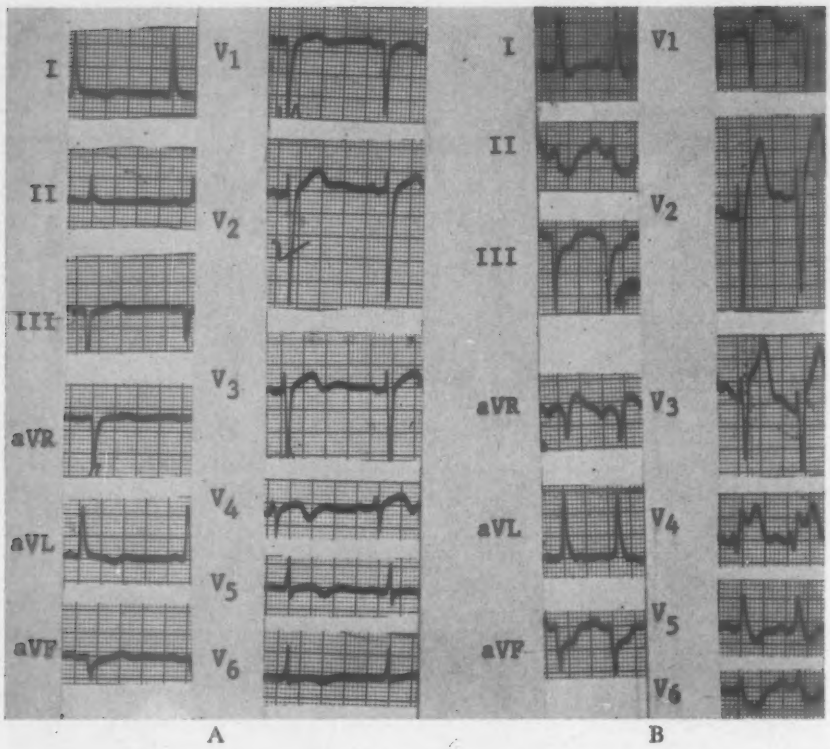



FIG. 2. A, January 7, five hours later. B, January 10. Both electrocardiograms reveal typical changes of anterior wall infarction.

2. In the presence of bundle branch block premature beats originate in the left ventricle late in diastole at the time the normal sinus excitation is due in the ventricles. The opposed effects of the dextrocardiogram (due to normal activation) and of the levocardiogram (due to the premature excitation) produce an approximately normal ventricular complex.

Simonson[7] reported also a case of left bundle branch block in which ventricular premature contractions and nodal escaped beats revealed the presence of "acute coronary insufficiency, probably infarction" which was obscured by the intraventricular block in the regular beats of sinus origin which were typical of left bundle branch block and not suggestive of infarction. Sommerville and Wood[4] have encountered "several" examples of this type in which the extrasystoles unmasked the signs of myocardial infarction obscured by the bundle branch block. Scherf and Schott[8] report three cases in which the extrasystoles were helpful in diagnosing myocardial infarction. Bellet[9] states that he has seen similar cases; in his book there is an electrocardiogram with R-T segment elevation suggesting acute myocardial infarction in the premature atrial contraction but not in the sinus beats; later there was definite evidence of the acute infarction in the sinus beats noted. This case is similar to our own case.

In contrast, Myers[10] has pointed out that the pattern in some extrasystoles may resemble that of myocardial infarction when this is not observed at autopsy; according to this author it is essential to be cognizant of such a possibility in the evaluation of distortion of the ventricular complex by ectopic beats, and to evaluate these extrasystoles in terms of the clinical findings.

Spang[3] reports a case with ventricular premature contractions in lead III revealing RS-T elevation suggestive of myocardial infarction. The signs of the infarction were clearer in the extrasystoles than in the basic rhythm. Spang theorizes that the diminished coronary blood flow during the extrasystolic contraction brings to the fore the "hidden damage."

Katz and his associates[1] reported two cases, suspected instances of myocardial infarction, in which the extrasystoles offered an early diagnostic clue and stated that this phenomenon might be more frequently encountered if the clinicians were alert to it. Soffer[11] described a case in which atrial premature contractions showed early the classical pattern of high lateral infarction while the sinus beats were non-revealing. Recently, Silverman and Salomon[12]

published a case in which some ventricular extrasystoles showed an old infarction pattern which was not clearly demonstrated in the normal sinus beats.


## Summary

Extrasystoles may offer an early or only clue to the recognition of a myocardial infarction, electrocardiographic signs of which lag or are obscured in the sinus beats. Another case is reported in which the extrasystoles offered the first objective evidence of the confirmed myocardial infarction.


## References


1. Katz, K. H., Berk, M. S. and Mayman, C. I. Acute myocardial infarction revealed in an isolated premature ventricular beat. *Circulation*, 18: 897, 1958.
2. Scherf, D. Extrasystoles. In: Cardiology, Encyclopedia of the Cardiovascular System. Volume 3, p. 11. Edited by Luisada, A. A. New York, 1959. McGraw-Hill.
3. Spang, K. Rhytmusstörungen des Herzens. Stuttgart, 1957. Georg Thieme Velag.
4. Sommerville, V. and Wood, P. Cardiac infarction with bundle branch block. *Brit. Heart J.*, 11: 305, 1949.
5. Dressler, W. A. A case of myocardial infarction masked by bundle branch block but revealed by occasional premature ventricular beats. *Am. J. M. Sc.*, 206: 361, 1943.
6. Wilson, F. M. and Herrmann, G. R. Experimental study of incomplete bundle branch block and refractory period of the heart of the dog. *Heart*, 8: 229, 1921.
7. Simonson, E., Enzer, N. and Goodman, J. S. Coronary insufficiency, revealed by ectopic nodal and ventricular beats in the presence of left bundle branch block. *Am. J. M. Sc.*, 209: 349, 1945.
8. Scherf, D. and Schott, A. Extrasystoles and Allied Arrhythmias. Melbourne, 1953. William Heinemann.
9. Bellet, S. Clinical Disorders of the Heart Beat. Philadelphia, 1953. Lea & Febiger.
10. Myers, G. B. Other QRS-T patterns that may be mistaken for myocardial infarction. IV. Alterations in blood potassium; myocardial ischemia; subendocardial myocarditis; distortion associated with arrhythmias. *Circulation*, 2: 75, 1950.
11. Soffer, A. The significance of serial "K" determinations and of certain premature contractions in acute myocardial injury. *Am. J. M. Sc.*, 237: 87, 1959.
12. Silverman, J. J. and Salomon, S. Myocardial infarction pattern discovered by ventricular extrasystoles. *Am. J. Cardiol.*, 4: 695, 1959.

# Progress Notes in Cardiology

*Edited by* EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

## Ebstein's Anomaly of the Tricuspid Valve

DRS. GEROLD L. SCHIEBLER, Paul Adams, Jr., Ray C. Anderson, Kurt Amplatz and Richard G. Lester (Departments of Pediatrics and Radiology, University of Minnesota Hospitals) have reviewed twenty-four cases of Ebstein's anomaly of the tricuspid valve. Eight of these twenty-four cases have had postmortem examination. This cardiac anomaly, occurring equally often in men and women, is thought by the authors to have an incidence of one in 50,000 to 100,000 births. Only one patient among the authors' cases had a relative with known congenital heart disease, but there is at least one report in the literature of this anomaly occurring in siblings.

Approximately a half of their patients had neonatal symptoms or signs, generally cyanosis, or a murmur. This neonatal cyanosis invariably diminished or disappeared with time, but recurred later in life in all cases. Ebstein's anomaly may interfere severely with fetal circulation, since some cases have been reported in stillborn infants.

Symptoms and signs after the neonatal period included dyspnea, cyanosis, excessive fatigue, central nervous system symptoms, cardiac failure, precordial or epigastric pain, paroxysmal tachycardia, and squatting. The most common physical findings were a systolic murmur, a second heart sound which was as well heard over the pulmonic area as over the aortic area, normal pulmonary breath sounds, cardiomegaly, normal growth features, a "triple" or "quadruple" heart rhythm, cyanosis, a "split" first sound, "metallic" or "clicking" heart tones, cardiac failure, and an unusual "facial erythema."

*Roentgen studies* regularly showed cardiomegaly, normal to decreased pulmonary vascularity, and a normal-sized left atrium. Cardiae size and contour varied widely, although in certain cases the "box-like" configuration was diagnostic. The most common *electrocardiographic abnormalities* in the nineteen patients with a normal sinoatrial rhythm were incomplete or complete right bundle branch block (often with widely splintered or notched complexes), peaked and occasionally prolonged P waves, low-voltage QRS complexes in the right precordial leads (none had an R wave in $V_1$ exceeding 8 mm. in height), and right axis deviation. Five cases showed a constant type B Wolff-Parkinson-White (WPW) pattern, and another did so intermittently. The presence of type B WPW pattern in a cyanotic child with congenital heart disease and normal to decreased pulmonary vascularity should immediately suggest the possibility of Ebstein's anomaly.

A total of twenty-one *right heart catheterizations* were carried out in these twenty-four patients, without any mortality or serious complications. The principal value of cardiac catheterization is in documenting the anomalous location of the tricuspid valve, and in obtaining pressure tracings in the various vessels and chambers. Although this tricuspid valve anomaly is usually associated with a valve-incompetent foramen ovale or an atrial septal defect causing a bidirectional shunt, it is important to be aware of the fact that this malformation has been found by others in association with ventricular septal defect, transposition of the great vessels, pulmonary stenosis and pulmonary atrisia. The cardiac catheter electrode is very useful because the recording of ventricular muscle potential simultaneously with an atrial pressure is pathognomonic of Ebstein's anomaly.

A new type of *surgical procedure* has been devised at this medical center by Hunter and Lillehei and has been used in two patients who were in terminal condition. Neither patient survived. Obviously, a trial in patients who are better risks will be required before the procedure can be properly evaluated.

The Ebstein anomaly may be confused with

an atrial septal defect of the ostium secundum type, pulmonary valvular stenosis, familial cardiomegaly, myocarditis, endocardial fibroelastosis, tetralogy of Fallot, tricuspid atresia or stenosis, rheumatic heart disease, pericardial effusion, or congenital tricuspid insufficiency.

Physiologic data and studies on postmortem specimens indicate that Ebstein's anomaly represents a continuum from predominant tricuspid stenosis to predominant tricuspid insufficiency, with some having elements of both, and others approaching normal.

# College News

## PRESIDENT'S COLUMN

## Dr. Paul Dudley White's Birthday

On JUNE 6, 1961 Dr. Paul Dudley White will be seventy-five years old. He is a man who understands the need for sentiment and the satisfaction that can come from remembering an event or an anniversary; I therefore hope that he will forgive this public birthday greeting.

There are few men who can feel so confident that their message has been heard and practiced. In every land there are physicians and patients who have in some manner been influenced by Dr. White. The scientific world of cardiology bears his permanent mark, but far beyond this there has been the priceless, perpetuating quality of marking young men. There are a host of men who identify themselves as PDW men and whose very lives have been changed by exposure to him. This has all been accomplished by the most subtle form of leadership . . . by personal enthusiasm, by hard work, and twenty-four hour a day diligence, by good humor, by kindliness, by small remembrances, by the ability to think well of others and thus gain the best from others, by accepting no restrictions from creed, race or politics.

I have spent the past several evenings reading through Dr. White's writings. Writing has been a skill which he exercised not only in his great text, but also in what might be termed more philosophic ways. A quotation from several of these can not only illustrate the beauty of phrase but also hint the reasons behind the love and affection which comes from all PDW men on his seventy-fifth birthday.

From the autobiographic comments of Dr. Paul Dudley White at his twenty-fifth year of graduation from Harvard College, June 1933:

"Work and play have both been delightful to me. The study of medicine and then, later, practice and teaching have exceeded all my earliest expectations. There has been a combined lure of adventuring on the frontier of our knowledge of the human body, of close contact with thousands of people of all ages and walks of life and of service, which is perhaps the most gratifying thing of all.

"The doctor's life is so full of excitement and interest, of pathos and humor, that it is not necessary to seek many diversions elsewhere. The chief danger is that of overwork and *therefore periods of rest and relaxation are essential.* These, I, myself, have secured by holiday adventuring in this country and abroad. Travel has thus been my greatest diversion. My wife and I have enjoyed especially many restful weeks and a little native wine in Southern Italy and Greece, where quiet, quiet contemplation has made us regret a bit the necessity of returning to the restless turmoil of America."

From the remarks on the occasion of becoming President of the American Heart Association, May 30, 1941, in Cleveland, Ohio, entitled "Cardiology as a Specialty":

"While still an intern I appreciated that it was impossible to do all of the things I should like to do in medicine. At first, I was very keen on obstetrics, and then on pediatrics. Later I thought I should like to be a practitioner or a professor of general medicine, or a dean. Then came the opportunity, and with it, a realization of the value of studying intensively in a special field, and so I selected cardiology with my eyes open, realizing that if I wanted to become well rounded in that field I could not spend so much time in other fields. It was plain as day and has continued to be so ever since. Patient perseverance during a good many years of preparation and of practice has brought me so much satisfaction and happiness that I am eternally grateful to the Fates for the advice I received in the beginning from those who steered me into this career and to those who have helped me to keep there, although I have been tempted frequently to do otherwise in this day and age of restless change.

". . . There is one other point I should like to mention, and that is the occasional remark one

hears about the narrowness of specialists. Of course, specialists may be narrow, but such a remark as a general observation is erroneous. Broad- or narrow-mindedness, philosophic points of view, and the value of the physician to his profession do not depend upon the particular kind of medical work that is being done; they depend upon the personality, training, industry, and environment of the individual. The family doctor may be broad- or narrow-minded, no matter how *extensive* his knowledge and experience may be; a specialist may be broad- or narrow-minded no matter how *intensive* his knowledge and experience may be. It is of prime importance, therefore, for the specialist as well as for the family doctor, to keep closely in touch with broad-minded associates in the field of medicine."

Quotation from a personal letter to Clarence William Lieb, M.D., dated March 10, 1953:

"... a close contact with colleagues, companions and friends, of whom a fair number should be younger in years, is a very desirable goal to cultivate. Among these comrades and friends, there should be included as many individuals as possible who have high spiritual ideals and sound philosophy rather than technical knowledge or social graces, or simply skills in work or play."

Dr. White! Happy Birthday!

E. GREY DIMOND, M.D.
*President*

# New Officers and Committees

ELECTION OF OFFICERS, 1961–1962

The following officers were elected for the year 1961–1962 at the Tenth Annual Meeting of the College on May 18, 1961 in New York City.

**President-Elect**

JOHN S. LADUE.....New York

**Vice-Presidents**

WILLIAM LIKOFF.....Pennsylvania
E. STERLING NICHOL.....Florida
STANLEY J. SARNOFF.....Maryland

**Secretary**

IRVING BROTMAN.....Washington, D. C.

**Asst.-Secretary**

HENRY A. ZIMMERMAN.....Ohio

**Treasurer**

HENRY I. RUSSEK.....New York

**Asst.- Treasurer**

LOUIS H. SIGLER.....New York

**Trustees for Five Years**

GEORGE C. GRIFFITH.....California
FRANCIS A. L. MATHEWSON.....Winnipeg, Canada
LAWRENCE E. LAMB.....Texas
RICHARD GORLIN.....Massachusetts

BOARD OF GOVERNORS

Dr. E. Grey Dimond, President, has announced the following new appointments to the Board of Governors of the College. The term of these State or Area Governors will expire in 1964.

State or Area Governors

**Kansas**
JAMES CROCKETT, M.D.....Kansas City

**Kentucky**
EDMUND D. PELLEGRINO, M.D.....Lexington

**Louisiana**
PHILIP H. JONES, M.D.....New Orleans

**Massachusetts**
RICHARD GORLIN, M.D.....Boston

**Minnesota**
C. WALTON LILLEHEI, M.D.....Minneapolis

**New Jersey**
NORMAN REITMAN, M.D.....New Brunswick

**New York (Metropolitan Area)**
ARTHUR GRISHMAN, M.D.....New York

**New York (Upstate Area)**
JOHN R. WILLIAMS, M.D.....Rochester

**North Dakota**
A. C. FORTNEY, M.D.....Fargo

**Ontario**
FORD CONNELL, M.D.....Kingston

**South Carolina**
WARREN IRVIN, M.D.....Columbia

**South Dakota**
JOHN L. CALENE, M.D.....Aberdeen

**Tennessee**
LAWRENCE GROSSMAN, M.D.....Nashville

**Virginia**
JOHN F. DAMMANN, M.D.....Charlottesville

**West Virginia**
ROBERT SONNEBORN, M.D.....Wheeling

NEW COMMITTEES 1961–1962

### Nominating Committee

*Chairman*
LAWRENCE E. LAMB, M.D. ..... Texas
*Members*
ELIOT CORDAY, M.D. ..... California
ABE RAVIN, M.D. ..... Colorado
ANTONI DIEHL, M.D. ..... Kansas

### Work Shop Committee

*Chairman*
SAMUEL BELLET, M.D. ..... Pennsylvania
*Members*
T. K. LIN, M.D ..... Honolulu, Hawaii
HADLEY CONN, M.D. ..... Pennsylvania
JAMES G. JANNEY, JR., M.D. ..... Missouri
THOMAS M. BLAKE, M.D. ..... Mississippi
C. FREDERICK KITTLE, M.D. ..... Kansas

### Scientific Program Committee

*Chairman*
WILLIAM L. MARTZ, M.D. ..... Indiana
*Members*
RICHARD GORLIN, M.D. ..... Massachusetts
C. FREDERICK KITTLE, M.D. ..... Kansas
ARTHUR GRISHMAN, M.D. ..... New York
BERNARD LOWN, M.D. ..... Massachusetts
OSCAR MAGIDSON, M.D. ..... California
IVAN D. BARONOFSKY, M.D. ..... California
JAMES E. CROCKETT, M.D. ..... Kansas
HADLEY CONN, M.D. ..... Pennsylvania
HERMAN HELLERSTEIN, M.D. ..... Ohio

### Endowed Lectureship Committee

*Chairman*
GEORGE MENEELY, M.D. ..... Tennessee
*Members*
CLARENCE M. AGRESS ..... California
DWIGHT E. HARKIN ..... Massachusetts
BENJAMIN M. GASUL ..... Illinois

### Publications Committee

*Chairman*
SIMON DACK ..... New York
*Members to be appointed*

### Convocation Committee

*Chairman*
LOUIS F. BISHOP ..... New York
*Members to be appointed*

### Awards Committee

*Chairman*
GEORGE R. MENEELY ..... Tennessee
*Members*
KENNETH G. KOHLSTAEDT ..... Indiana
TRAVIS G. WINSOR ..... California
LOUIS F. BISHOP ..... New York

### Respiratory-Cardiac Failure Committee

*Chairman*
CLAUDE S. BECK ..... Ohio
*Members*
PALUEL J. FLAGG ..... New York
ROBERT M. HOSLER ..... Ohio
DAVID S. LEIGHNINGER ..... Ohio
GEORGE R. MENEELY ..... Tennessee

### Overseas Educational Program Committee

*Chairman*
ELIOT CORDAY ..... California
*Members*
OSLER A. ABBOTT ..... Georgia
GEORGE W. CALVER ..... Washington, D. C.
PHILIP REICHERT ..... New York
E. GREY DIMOND ..... California

### Budget and Finance Committee

*Chairman*
OSLER A. ABBOTT ..... Georgia
*Members*
PHILIP REICHERT ..... New York
GEORGE W. CALVER ..... Washington, D. C.

### Convention Arrangements Committee

*Chairman*
GEORGE W. CALVER ..... Washington, D. C.

### State Department Contact Committee

*Chairman*
GEORGE W. CALVER ..... Washington, D. C.

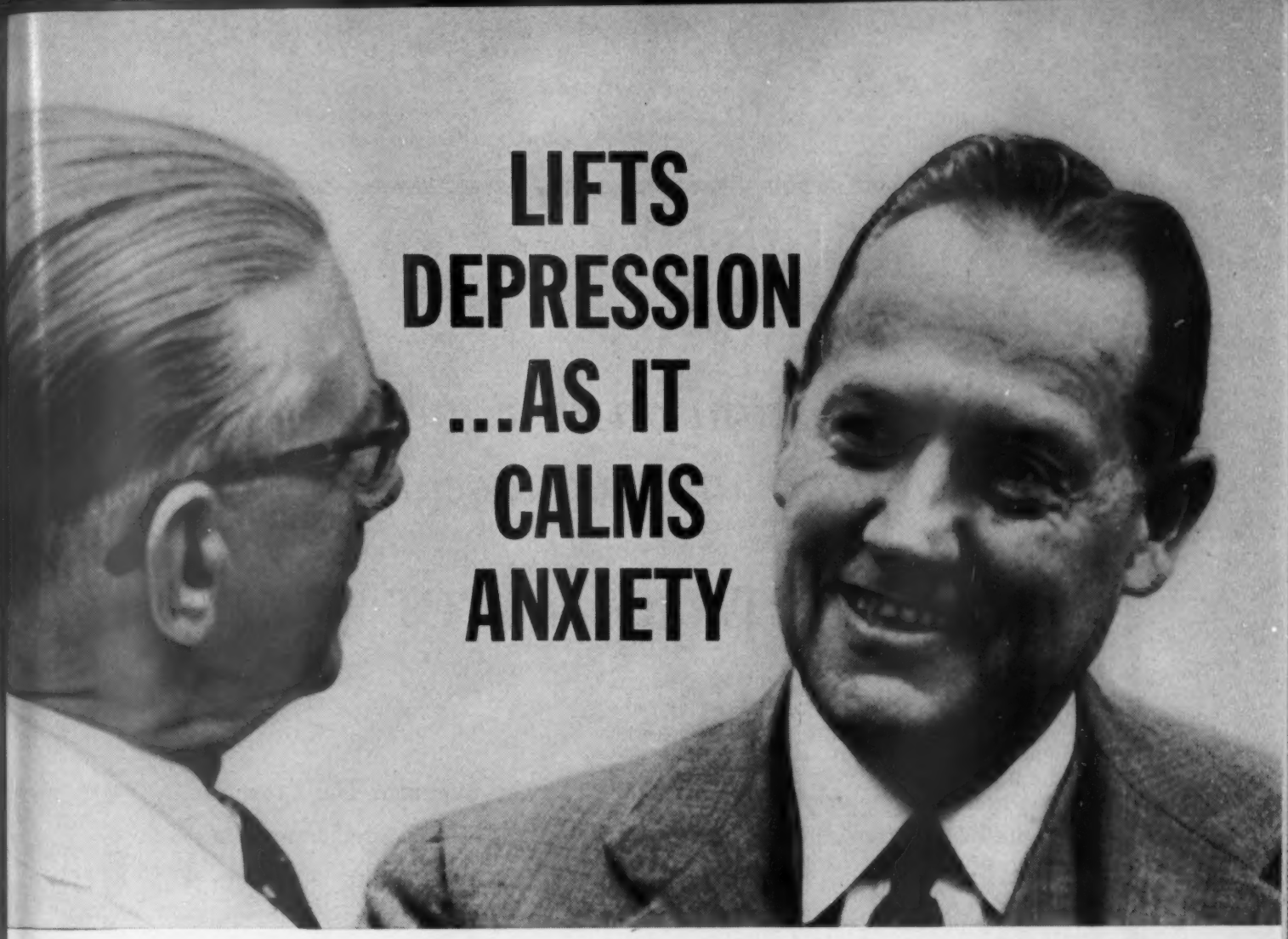
# AUTHOR INDEX VOLUME VII

# SUBJECT INDEX VOLUME VII

(ab.) = Abstracts; (CCC) = Clinical Case Conference; (CR) = Cardiac Resuscitation; (DS) = Diagnostic Shelf; (E) = Editorial; (HM) = Historical Milestones; (LE) = Letter to the Editor; (PN) = Progress Notes in Cardiology; (QC) = Query Corner; (WC) = Workmen's Compensation




January (pp. 1–160); February (pp. 161–314); March (pp. 315–470); April (pp. 471–628); May (pp 629–768); June (pp. 769–898)




**Thanks to your balanced Deprol therapy**... his depression has lifted and his mood has brightened up – while his anxiety and tension have been calmed down. He sleeps better, eats properly, and normal drive and interest have replaced his emotional fatigue.

## Brightens up the mood, brings down tension

*Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines.* While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

*Acts rapidly – you see improvement in a few days.* Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

**Compatible with therapy for physical diseases.** Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver toxicity, hypotension or tachycardia.

# ▲Deprol▲®

**Dosage:** Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
**Composition:** 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
**Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.

WALLACE LABORATORIES / *Cranbury, N. J.*

CD-4489


# *A measure of man's progress...*

*...has always been the specificity of his tools. Just as crude stone axes represented progress in primitive times, electronic calculators reflect the intellectual advancement of modern man. In recent years, however, scientific investigation has been so fruitful that specialized devices often could not keep pace. This "instrument lag," for example, has been noted in cardiovascular medicine.*

*In recognition of recent scientific advances and the pressing need for special instrumentation, Becton, Dickinson and Company has originated a* CARDIOVASCULAR AND SPECIAL INSTRUMENTS SERVICE *whose chief function is to make new instruments rapidly available for this vitally important area of medicine.*

*Special research and development facilities have been created. A team of Becton-Dickinson specialists is devoting its full attention to the development of unique and experimental devices. But we believe today, as in the past, that it is you—the man behind the instrument—who knows best what changes or innovations are needed. Because this service can work only through a full, continuous partnership, we hope you will comment and make suggestions.*

*B-D would like to send you an illustrated catalog describing various products available for radiology, cardiovascular work, and cardiac surgery. Simply complete and mail coupon.*

Becton, Dickinson and Company
Cardiovascular and Special Instruments Service
Dept. A-6
Rutherford, New Jersey

Please send me your Cardiovascular Product Catalog.

NAME_____, M.D.

ADDRESS_____

CITY_____ ZONE____ STATE_____

**csi**-CARDIOVASCULAR AND SPECIAL INSTRUMENTS SERVICE

B-D BECTON, DICKINSON AND COMPANY
RUTHERFORD, NEW JERSEY

*Brockenbrough needle for transseptal left heart catheterization —18 gauge (regular wall), 71 cm. long.

B6761

*An instructive new seminar*

*that presents recent clinical findings on*

# MYCOTIC INFECTIONS

*This seminar contains:*

**Current Concepts of Diagnostic Serology and Skin Hypersensitivity in the Mycoses.**

S. B. SALVIN, PH.D., *Hamilton, Montana.*

From the U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institutes of Allergy and Infectious Diseases, Rocky Mountain Laboratory, Hamilton, Montana.

**The Course and Prognosis of Histoplasmosis.**

HARRY RUBIN, M.D., MICHAEL L. FURCOLOW, M.D., *Kansas City, Kansas,* J. LEWIS YATES, M.D. and CHARLES A. BRASHER, M.D., *Mount Vernon, Missouri.*

From the Kansas City Field Station, Communicable Disease Center, Bureau of State Services, Public Health Services, U.S. Department of Health, Education, and Welfare, University of Kansas School of Medicine, Kansas City, Kansas, and the Missouri State Sanatorium, Mount Vernon, Missouri.

**Aspergillosis. A Review and Report of Twelve Cases.**

SYDNEY M. FINEGOLD, M.D., DRAKE WILL, M.D. and JOHN F. MURRAY, M.D., *Los Angeles, California.*

From the Department of Medicine, Wadsworth Hospital, Veterans Administration Center, Los Angeles, and Department of Medicine and Pathology, University of California Medical Center, Los Angeles, California.

**The Use of Amphotericin B in the Treatment of Coccidioidal Disease.**

WILLIAM A. WINN, M.D., *Springfield, California.*

From the Department of Medicine, Tulare-Kings Counties Hospital, Springville, California.

**North American Blastomycosis.**

E. RICHARD HARRELL, M.D. and ARTHUR C. CURTIS, M.D., *Ann Arbor, Michigan.*

From the Department of Dermatology, University of Michigan Medical Center, and the V.A. Hospital, Ann Arbor, Michigan.

**Cryptococcosis (Torulosis). Current Concepts and Therapy.**

M. L. LITTMAN, M.D., PH.D., *New York, New York.*

From the Departments of Microbiology and Medicine, the Mount Sinai Hospital, New York, N. Y. These studies were supported in part by research grants from the Squibb Institute for Medical Research and the National Science Foundation.

**Actinomycosis and Nocardiosis. A Review of Basic Differences in Therapy.**

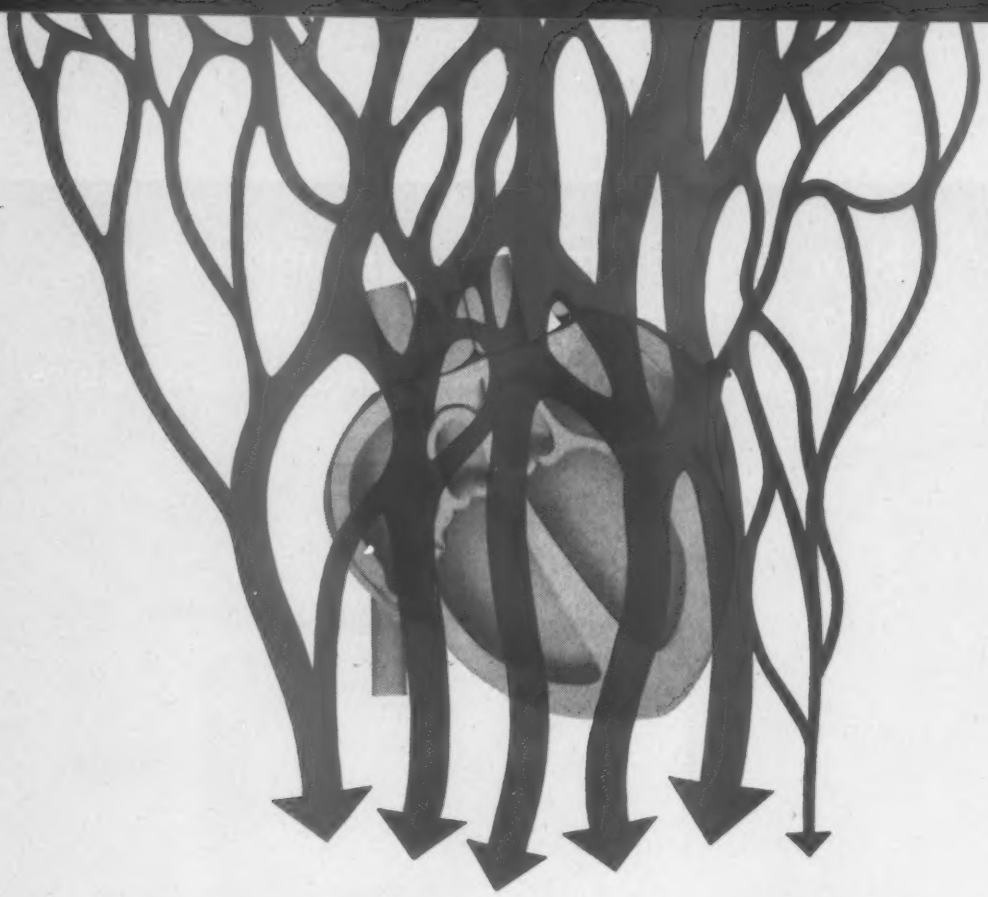
JOSEPH W. PEABODY, JR., M.D., *Washington, D.C.,* and JOHN H. SEABURY, M.D., *New Orleans, Louisiana.*

*[Fully illustrated—Many references included]*

The Seminar on Mycotic Infections originally appeared in The American Journal of Medicine and is now available in bound library reference form at $3.00 per copy.

THE AMERICAN JOURNAL OF MEDICINE

466 Lexington Avenue • New York 17, N. Y.



# POTENT CORONARY VASODILATOR PRODUCES GOOD RESPONSE IN 82.7% OF PATIENTS[1]

**ISORDIL "...appears to exert a more consistent and profound effect than any drug previously employed for the prophylaxis of angina pectoris...Rapid onset of action and prolonged effect are additional clinical advantages."[1]**

Isordil "...has been effective in about three-fourths of 51 patients with severe angina. Thirty-nine of the patients experienced either disappearance of the pain symptoms or substantial reduction in frequency and duration of attacks."[2]

Patients showed a dramatic decrease in the incidence and severity of angina pectoris and reported an increased sense of well being and a notable increase in exercise tolerance.[1]

Isordil's "...long duration of action and consistent marked activity establishes it as a most reliable drug for maintenance of dilatation of coronary vessels."[3]

Isordil "...appears to be the only agent currently available with marked sublingual as well as oral antianginal effectiveness."[4]

Dosage: average dose one 10 mg. tablet q.i.d.—a half hour before meals and at bedtime; dosage range 5-30 mg. q.i.d.; individualize dose for optimum therapeutic effect; use with caution in patients with glaucoma. Supplied: 10 mg. scored white tablets in bottles of 100.

1. Albert, A.: Isosorbide Dinitrate in Treatment of Angina Pectoris, Journal Lancet, *81*:112 (March) 1961. 2. Shapiro, S.: Angina Pectoris: Treatment with Isosorbide Dinitrate, Angiology *12*:53 (Feb.) 1961. 3. Leslie, R. E.: Coronary Vasodilators—A Comparative Study, Western Medicine *2*:56 (Feb.) 1961. 4. Russek, H. I.: Comparative Responses to Various Nitrates in the Treatment of Angina Pectoris, Journal of the Kansas City Southwest Clinical Society *36*:14 (Dec.) 1960.

# ISORDIL®

**FOR ANGINA PECTORIS**

ISOSORBIDE DINITRATE

**NOW AVAILABLE: ISORDIL WITH PHENOBARBITAL, THE ACCEPTED SEDATIVE FOR THE RELIEF OF ANXIETY IN HEART PATIENTS.**

IVES IVES-CAMERON COMPANY
New York 16, N. Y.

Literature and Professional Samples Available on Request

*TRADEMARK

# Hygroton®

brand of chlorthalidone

## in hypertension and edema, longer in action smoother in effect

Longer action[1] provides smooth, evenly-sustained therapeutic effect.[2] ■ Potent antihypertensive properties facilitate effective treatment of hypertension, frequently without auxiliary agents.[3] ■ Safeguards against significant potassium loss.[4] ■ Intensity of saluretic action enables liberalization of dietary salt restriction.[3] ■ Simplified dosage schedule affords economy of maintenance on just 3 doses per week.[2]

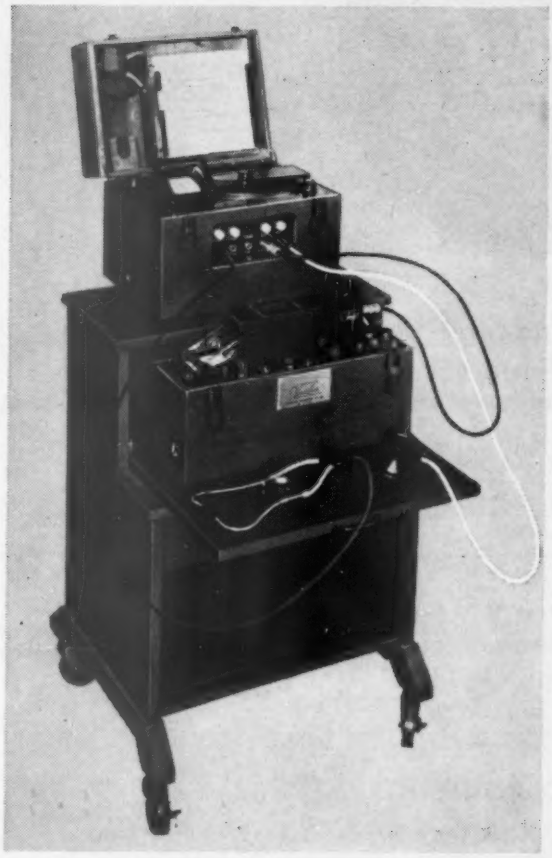
References: 1. Ford, R. V.: Current Therap. Research 2:347, 1960. 2. Fuchs, M., and others: Current Therap. Research 2:11, 1960. 3. Ford, R. V.: Connecticut Med. 24:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. 56:343, 1960.

Detailed literature available on request.

Hygroton®, brand of chlorthalidone, is available as white, single-scored tablets of 100 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York HY573-61 Geigy

# To Aid the Cardiologist in making MORE ACCURATE · MORE COMPLETE Diagnosis of Heart Disease



THE CAMBRIDGE AUDIO-VISUAL HEART SOUND RECORDER AND THE CAMBRIDGE VERSA-SCRIBE ELECTROCARDIOGRAPH

shown mounted on a special space-saving Two-Tier Table.

## CAMBRIDGE AUDIO-VISUAL HEART SOUND RECORDER

With this portable instrument the Doctor hears the amplified heart sounds through binaural ear phones, while he views their pattern on a long persistence cathode tube screen. What he sees and hears may be permanently recorded on a paper-thin magnetic disc. Such records may be filed with the patient's history, mailed to a consultant or played back for future study.

## CAMBRIDGE VERSA-SCRIBE ELECTROCARDIOGRAPH

This accurate, portable direct-writing instrument has the CAMBRIDGE dual paper speed feature. The operator can double the speed of paper travel by simply throwing a switch. This is especially valuable when high accuracy is required for measuring intervals upon electrocardiograms showing rapid heart rates or those having notching and splintering.

*While both of these fine instruments are effectively used independently, when used together they provide a new and valuable approach to the more accurate and complete diagnosis of heart disease. Let us give you further information about them.*

*Send for bulletins #185 and #188VS*

**CAMBRIDGE**
**DIAGNOSTIC INSTRUMENTS**

**CAMBRIDGE INSTRUMENT CO., INC.**

**Graybar Building, 420 Lexington Ave., New York 17, N. Y.**

| Cleveland 2, Ohio | Detroit 37, Mich. | Oak Park, Ill. | Jenkintown, Pa. | Silver Spring, Md. |
|---|---|---|---|---|
| 8419 Lake Avenue | 13730 W. Eight Mile Rd. | 6605 West North Avenue | 479 Old York Rd. | 933 Gist Avenue |

*PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH*

**CHANGING YOUR ADDRESS?**

Please fill out and return the coupon below:

---

**THE AMERICAN JOURNAL OF CARDIOLOGY**
Mailing Dept., 466 Lexington Avenue, New York 17, N. Y.

NAME_____
(please print)

NEW ADDRESS:

Street_____

City_____ Zone_____ State_____

FORMER ADDRESS:

Street_____

City_____ Zone_____ State_____

Schering

# over 5 years of clinical studies ...and 4 years of animal studies have confirmed the advantages of

# Miradon®

anisindione

## in short- or long-term anticoagulant therapy

*prompt, predictable, reproducible results* • "leads to an initial rapid fall in prothrombin activity...."[1] Therapeutic levels attained in 48 to 72 hours • achieves "a rather uniform and predictable fall in prothrombin activity."[2] • "Results are reproducible."[3]

*easy reversibility...and prompt restoration of effect* • vitamin $K_1$ "counteracted the effect of MIRADON in a predictable fashion in 5 to 8 hours."[4] • "The anticoagulant effect can be restored rapidly by remedication."[1]

*"even-keel" stability in maintenance therapy* • "Once the prothrombin levels had been reduced to the therapeutic bracket, they were maintained there with little difficulty on daily doses of the drug...."[5]

*Packaging:* MIRADON Tablets, 50 mg., bottles of 100. For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

*References:* (1) Lange, K., *et al.:* Am. Heart J. *55*:73, 1958. (2) Lange, K., *et al.:* Anisindione: A new improved anticoagulant, Scientific Exhibit, 106th Ann. Meet., A.M.A., New York, June 3-7, 1957. (3) Blaustein, A.: New York J. Med. *58*:701, 1958. (4) Connell, W. F., and Mayer, G. A.: Canad. M.A.J. *80*:785, 1959. (5) Paul, H. A., *et al:* Surg. Gynec. & Obst. *108*:605, 1959.

S-821

# extends the usefulness of Vitamin $K_1$ therapy†...

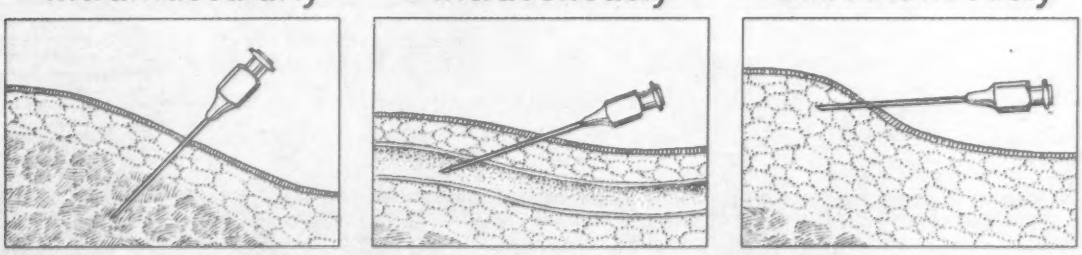
NEW Injection

# AquaMEPHYTON

AQUEOUS COLLOIDAL SOLUTION

†a clear, stable, aqueous colloidal solution for administration

• intramuscularly • intravenously • subcutaneously



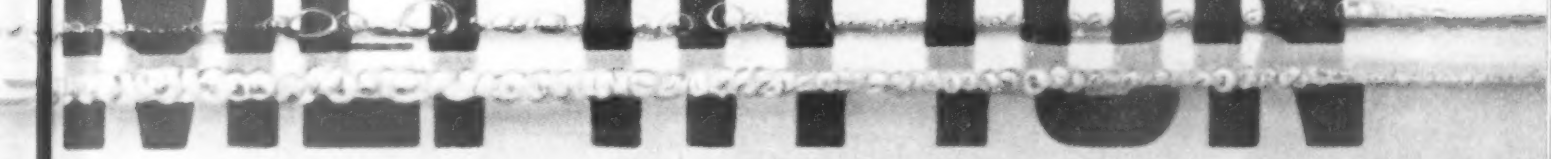
a dosage form for every Vitamin K indication:

AquaMEPHYTON (for intramuscular, intravenous, subcutaneous administration), 1-cc. ampuls containing 10 mg. MEPHYTON, Vitamin $K_1$

TABLETS MEPHYTON (for oral administration), 5 mg.

EMULSION MEPHYTON (for intravenous administration only), 1-cc. ampuls containing 10 mg. and 50 mg. per cc.

# MEPHYTON®



OF MEPHYTON®, VITAMIN $K_1$

*Vitamin $K_1$ "has a more prompt, more potent and more prolonged effect than the vitamin K analogues"* *

*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1960, p. 732

## reduces the hazard of hemorrhage due to hypoprothrombinemia in:

- prophylaxis and therapy of hemorrhagic disease of the newborn
- surgery, preoperatively and postoperatively
- anticoagulant-induced prothrombin deficiency
- inadequate absorption of Vitamin K
- biliary tract disease
- prothrombin-depressing drugs such as salicylates and phenylbutazone
- inadequate endogenous production of Vitamin K

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

**MERCK SHARP & DOHME**
**DIVISION OF MERCK & CO., INC., WEST POINT, PA.**

# For long-term control of hypertension, all the benefits of thiazide-rauwolfia therapy ...plus specific, physiologic vasodilation

**Protoveratrine A vasodilation produces "the most physiologic, hemodynamic reversal of hypertension."[1]** Only Salutensin offers your patient the advantages of protoveratrine A, a specific vasodilating agent, in combination with basic thiazide-rauwolfia therapy. Protoveratrine A is credited with producing "the most physiologic, hemodynamic reversal of hypertension."[1] It acts on the blood pressure reflex receptors[2-5] in the carotid sinus, heart and aorta to produce widespread peripheral vasodilation, increase renal blood flow, and relieve tachycardia. Because of the potentiating effect of Saluron, the diuretic component in Salutensin, the quantity of protoveratrine A in Salutensin is small enough to eliminate or reduce to a minimum the risk of unpleasant "veratrum" side effects.

**A logical combination of actions, a single result: antihypertensive potentiation with reduced side effects.** With Salutensin, you can resolve the problem of treating hypertension by means of this more logical antihypertensive approach—antipressor diuresis, mild sedation and specific peripheral vasodilation. Salutensin combines Saluron, a more effective 'dry-weight' diuretic which produces up to 60% greater excretion of sodium than does chlorothiazide;[9] reserpine, for mild tranquilizing and vasorelaxant effects; and protoveratrine A, to relieve arteriolar constriction and reduce peripheral resistance. The potentiating/additive effects of these antihypertensive agents[6,7,8,10-13] have been found to give a greater total therapeutic effect at dosage levels of each agent which *reduce the incidence and severity* of their side reactions.

**Added advantages for long-term or difficult patients.** Salutensin is indicated for almost every patient with essential hypertension who requires treatment. It will reduce blood pressure (both systolic and diastolic) to normal or near-normal levels, *and maintain it there,* in the great majority of cases. Patients on thiazide/rauwolfia therapy often experience further improvement when transferred to Salutensin. Patients who no longer respond to thiazide/rauwolfia may be spared the disturbing side effects of more potent antihypertensives by transferring them to Salutensin or by using Salutensin as their basic regimen. And Salutensin therapy is economical and convenient.

***Each Salutensin tablet contains:*** 50 mg. Saluron (hydroflumethiazide), 0.125 mg. reserpine, and 0.2 mg. protoveratrine A. See Official Package Circular for complete information on dosage, side effects and precautions.

***Supplied:*** Bottles of 60 scored tablets.

***References:*** 1. Fries, E. D.: In Hypertension, ed. by J. H. Moyer, Saunders, Phila., 1959, p. 123. 2. Brest, A. N. and Moyer, J. H.: *J.A.M.A. 172*:1041 (Mar. 5) 1960. 3. Grollman, A.: *Pharmacology and Therapeutics,* Lea & Febiger, Phila., 1960, p. 482. 4. Winer, B. M.: *Circulation 22*:1074 (Dec.) 1960. 5. Martz, B. L.: *J. Indiana M. A. 52*:1779 (Oct.) 1959. 6. Fries, E. D.: *South M. J. 51*:1281 (Oct.) 1958. 7. Finnerty, F. A. and Buehholz, J. H.: *GP 17*:95 (Feb.) 1958. 8. Gill, R. J., *et al.: Am. Pract. & Digest Treat. 11*:1007 (Dec.) 1960. 9. Ford, R. V. and Nickell, J.: *Ant. Med. & Clin. Ther. 6*:461, 1959. 10. Brest, A. N. and Moyer, J. H.: *J. South Carolina M. A. 56*:171 (May) 1960. 11. Wilkins, R. W.: *Postgrad. Med. 26*:59 (July) 1959. 12. Gifford, R. W., Jr.: Read at the Hahnemann Symp. on Hypertension, Phila. Dec. 8 to 13, 1958. 13. Fries, E. D., *et al.: J.A.M.A. 166*:137 (Jan. 11) 1958.

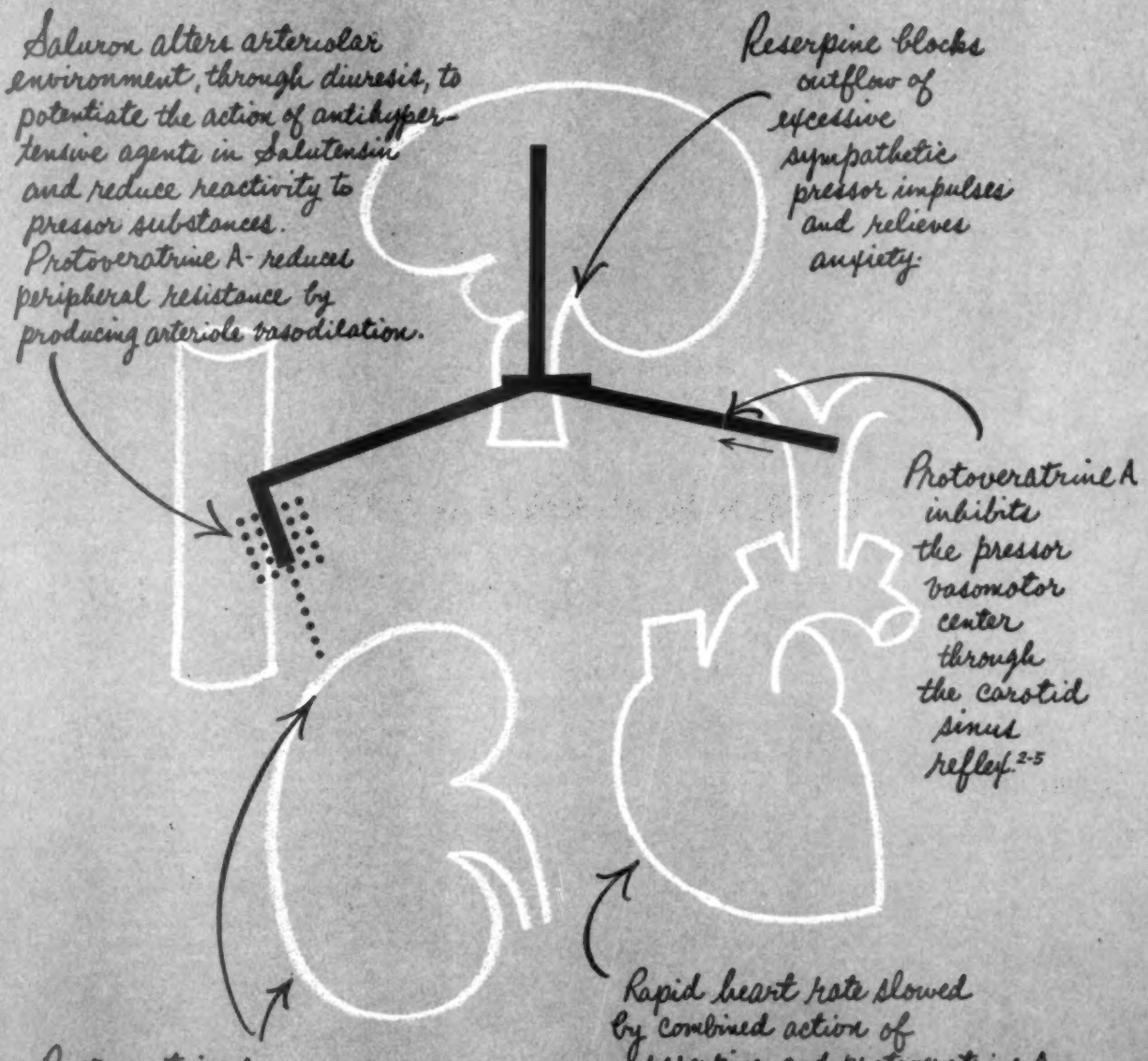
# SALUTENSIN®

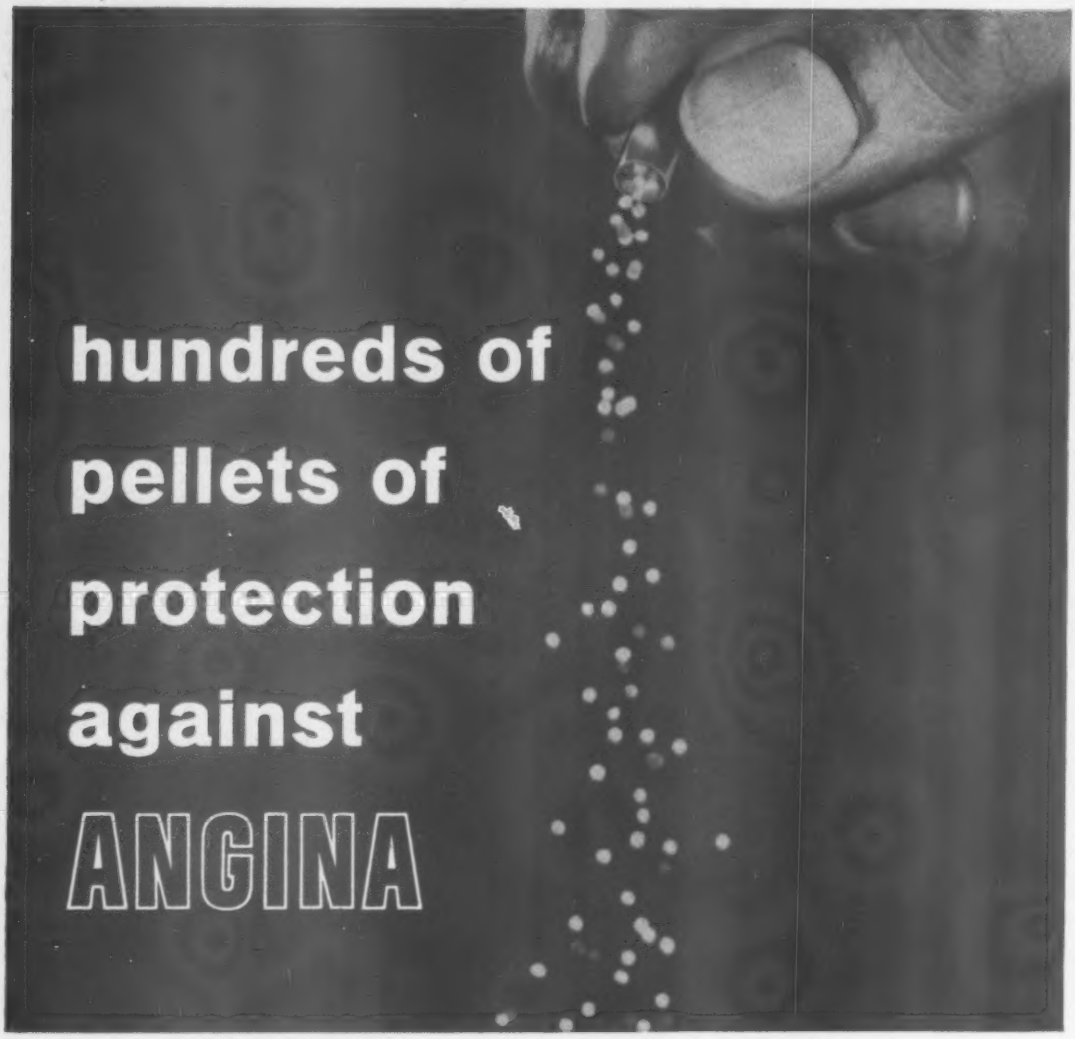
(hydroflumethiazide, reserpine, protoveratrine A—antihypertensive formulation)

BRISTOL LABORATORIES
Division of Bristol-Myers Co. / Syracuse, N.Y.

Also available—for edema, hypertension...when a thiazide alone is enough:
SALURON®(hydroflumethiazide) the 'dry-weight' diuretic with long-term benefits

# Salutensin - What it does






# PENTRITOL® TEMPULES

controlled disintegration capsules

**A single 30 mg. Pentritol Tempule with 12 hour action exhibits an even nitrite release which "tends to produce a smooth, prolonged response similar to that of the sustained release of modern depot injections."[1] Duration, frequency, and severity of anginal attacks are markedly lessened. Patients showing little progress during years of therapy with 80 mg. daily of PETN tablets, respond favorably to the smaller dose of Pentritol Tempules.[2] Kamil and Klinger report the response of their patients to a timed-disintegration pentaerythritol tetranitrate capsule as excellent, with nitroglycerin requirements reduced as much as 85%.[3]**

1. Biegeleisen, H. I.: Clin. Med. *2*:1006, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.

**PENTRITOL**

Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective therapy for and prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown superior results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity for physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol®-B Tempules®, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS • *Armour Means Protection*

*from the leader in cardiac resuscitation instrumentation*

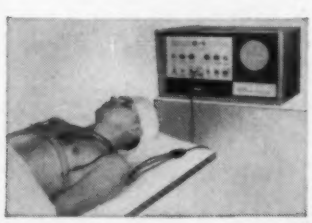

*new pre-eminence in the prevention, detection and automatic treatment of Cardiac Arrest*

# the Electrodyne PMS-5

**Proudly we present our latest and most refined instrument for the prevention, detection and automatic treatment of ventricular standstill through the application of efficacious electrical impulses through the intact chest or directly to the heart.**

Engineered for unexcelled valuable time-saving simplicity of operation, only Electrodyne offers an instrument of this type. Monitoring heart action visually and audibly, it instantly signals Cardiac Arrest and automatically provides external stimulation. Any Cardiac Arrhythmia is instantly recognizable on the highly visible large 5" Electrocardioscope which presents a continuous display of the electrocardiogram.

Please write for an informative file of technical specifications on this and other fine Electrodyne equipment.



- *Only Electrodyne offers an instrument of this type.*
- *Full 5" electrocardioscope for greater visibility.*
- *Simplicity of operation, functional appearance.*

***Electrodyne Company, Inc.***
***20 Endicott Street, Norwood, Massachusetts, U. S. A.***

**The reputation of Electrodyne instruments has established leadership in the field of medical electronics for the preventive detection and treatment of Cardiac Standstill, Ventricular Fibrillation and Cardiac Arrhythmias.**

"nutrition . . . present as a modifying or complicating factor in nearly every illness or disease state."[1]

# Theragran®

SQUIBB VITAMINS FOR THERAPY

*clinically-formulated and potency-protected vitamins for your patients with cardiac disease who need therapeutic vitamin support*

"Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2]

*Each Theragran supplies the essential vitamins in truly therapeutic amounts:*

| | |
|---|---|
| Vitamin A | 25,000 U.S.P. Units |
| Vitamin D | 1,000 U.S.P. Units |
| Thiamine Mononitrate | 10 mg. |
| Riboflavin | 10 mg. |
| Niacinamide | 100 mg. |
| Vitamin C | 200 mg. |
| Pyridoxine Hydrochloride | 5 mg. |
| Calcium Pantothenate | 20 mg. |
| Vitamin $B_{12}$ | 5 mcg. |

For full information see your Squibb Product Reference or Product Brief.

1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958.
2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

SQUIBB *Squibb Quality—the Priceless Ingredient*

# 5-year study[1] with COUMADIN demonstrates: long-term anticoagulation in office management of outpatients is practical and effective

A 5-year study[1] of long-term anticoagulation with COUMADIN (warfarin sodium) in office practice patients has demonstrated that such treatment reduces the probability of further infarctions in the postinfarct patient and is effective in preventing a first infarction in patients with angina.

An earlier report[2] noted that long-term anticoagulant therapy with warfarin sodium can be carried out, along with the necessary prothrombin time determinations, as part of general office practice.

**"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of Warfarin sodium [COUMADIN]."[1]**

**COUMADIN®**
FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

**the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant[3,4] and as "the best anticoagulant available today."[5] Over 179,000,000 doses administered to date.**

## *the proven anticoagulant for long-term maintenance*

**Full range of oral and parenteral dosage forms**—COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

**Average Dose:** Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:118, Sept. 10, 1960. 3. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 4. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958.

*Manufactured under license from the Wisconsin Alumni Research Foundation

*Complete Information and Reprints on Request* Endo **ENDO LABORATORIES** Richmond Hill 18, New York

# NEW BOOKS FOR THE CARDIOLOGIST

☐ *E. Grey Dimond*—**THE EXERCISE ELECTROCARDIOGRAM IN OFFICE PRACTICE.** Pub. July '61

☐ *Dale Groom*—**CLINICS IN ELECTROCARDIOGRAPHY.** Pub. Oct. '60, 160 pp., 398 il., $8.00

☐ *William C. Holland and Richard L. Klein*—**CHEMISTRY OF HEART FAILURE.** Pub. Aug. '60, 132 pp., 24 il. (Amer. Lec. Living Chemistry), $5.50

☐ *Carl Hughes and Warner Bowers*—**TRAUMATIC LESIONS OF PERIPHERAL VESSELS.** Pub. Feb. '61, 208 pp., 110 il., $8.00

☐ *Vernon M. Ingram*—**HEMOGLOBIN AND ITS ABNORMALITIES.** Pub. April '61, 168 pp., 93 il. (Amer. Lec. Living Chemistry), $7.50

☐ *S. D. Larks*—**FETAL ELECTROCARDIOGRAPHY.** Pub. Nov. '60, 128 pp. ($6^3/_4 \times 9^3/_4$), 70 il. (Amer. Lec. Gynecology and Obstetrics), $6.50

☐ *James W. Linman and Frank H. Bethell*—**FACTORS CONTROLLING ERYTHROPOIESIS.** Pub. Aug. '60, 224 pp., 58 il. (Amer. Lec. Hematology), $8.25

☐ *M. Judson Mackby*—**THE SURGICAL TREATMENT OF PORTAL HYPERTENSION, BLEEDING ESOPHAGEAL VARICES AND ASCITES.** Pub. Aug. '60, 277 pp., 49 il. (2 full color plates), (Amer. Lec. Surgery), $10.50

☐ *Rudolf Nissen and Roger H. L. Wilson*—**PAGES IN THE HISTORY OF CHEST SURGERY.** Pub. Nov. '60, 176 pp., 90 il., $7.50

☐ *George Pickering*—**THE TREATMENT OF HYPERTENSION.** Pub. March '61, 192 pp., 70 il. (Amer. Lec. Living Chemistry), $7.00

☐ *O. D. Ratnoff*—**BLEEDING SYNDROMES: A Clinical Manual.** Pub. Nov. '60, 288 pp., 7 il. (Amer. Lec. Circulation), $8.50

☐ *Gus Schreiber*—**EMBOLIC DISPERSOIDS IN HEALTH AND DISEASE.** Pub. Sept. '60, 104 pp., 12 il. (Amer. Lec. Living Chemistry), $5.50

☐ *Merle E. White*—**AN OUTLINE GUIDE FOR THE CARE OF POST-OPERATIVE CARDIAC PATIENTS.** Pub. April '61, 120 pp., 75 il., $6.00

☐ *W. Carleton Whiteside*—**TOWARD THE DIAGNOSIS OF CONGENITAL HEART DISEASE.** Pub. Oct. '60, 100 pp., $4.50

☐ *Michael Woodruff*—**THE TRANSPLANTATION OF TISSUES AND ORGANS.** Pub. Sept. '60, 816 pp. ($7 \times 10$), 336 il. (1 in full color), $25.50

☐ *Grace Wyshak, Leonid S. Snegireff and Augusta F. Law*—**CARDIACS AND DIABETICS IN INDUSTRY: A Study in Work Experience.** Pub. July '61

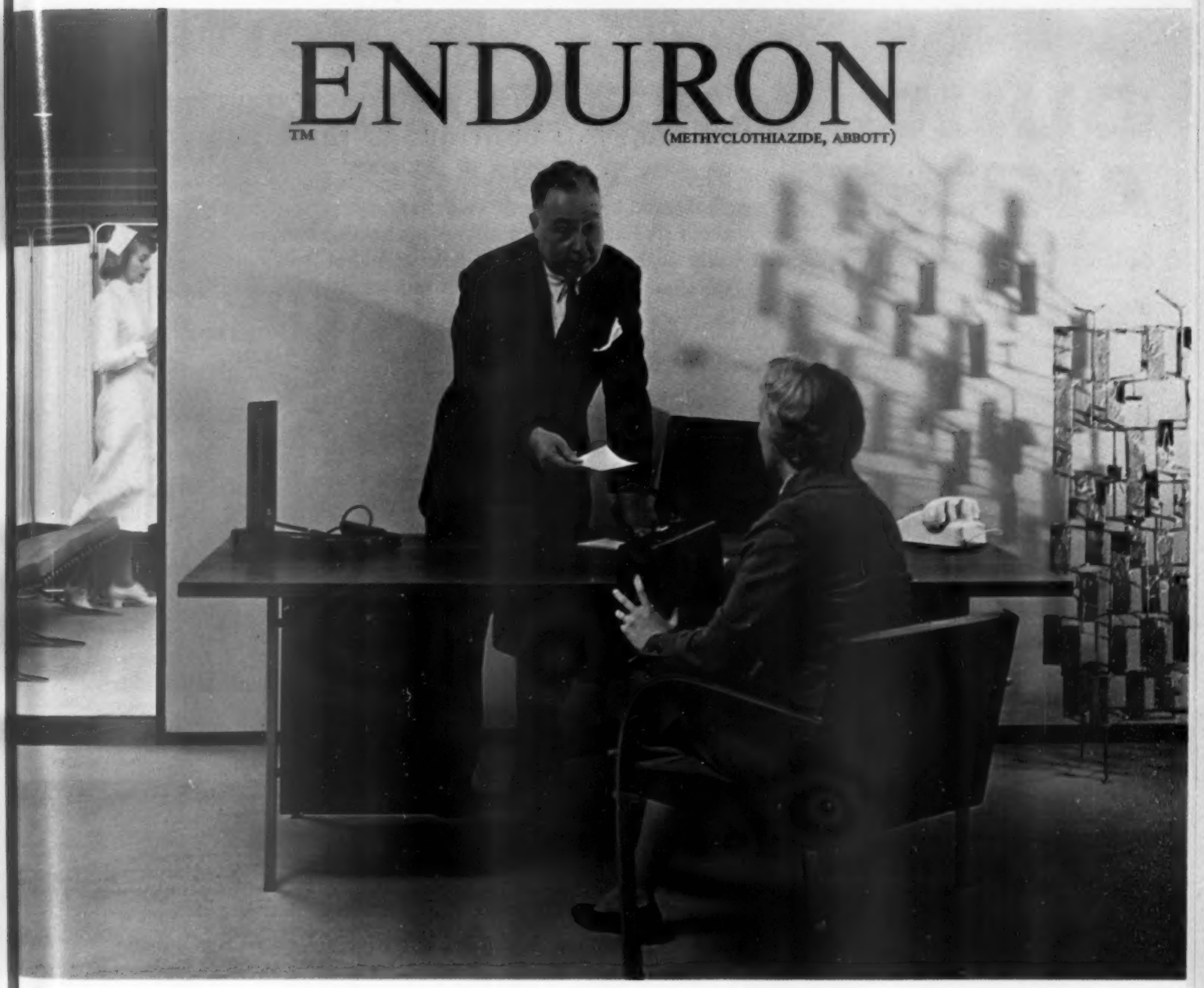
☐ *J. M. Yoffey*—**QUANTITATIVE CELLULAR HEMATOLOGY.** Pub. Oct. '60, 144 pp., 17 il. (2 in full color plates), (Amer. Lec. Hematology), $5.50

**CHARLES C THOMAS • PUBLISHER** 301-327 East Lawrence Avenue **SPRINGFIEED • ILLINOIS**

The 24-hour diuretic-antihypertensive

# ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)



## Nothing is simpler in thiazide therapy: Prescribe "Enduron once a day, every day"

One dose daily of this potent new thiazide is ample. It treats edema and hypertension around the clock. You can expect therapeutic action through the full 24 hour period (and longer).

What's more, Enduron provides an enhanced potassium-sparing effect. Whereas multiple dose drugs may cause multiple peaks of potassium loss, Enduron's single dose brings but a temporary single peak.

Enduron's once-a-day dosage is of course a convenience, too. Easy for the patient to remember. Easy for you to supervise. We invite you to experience its benefits . . . soon. *(See next page)*

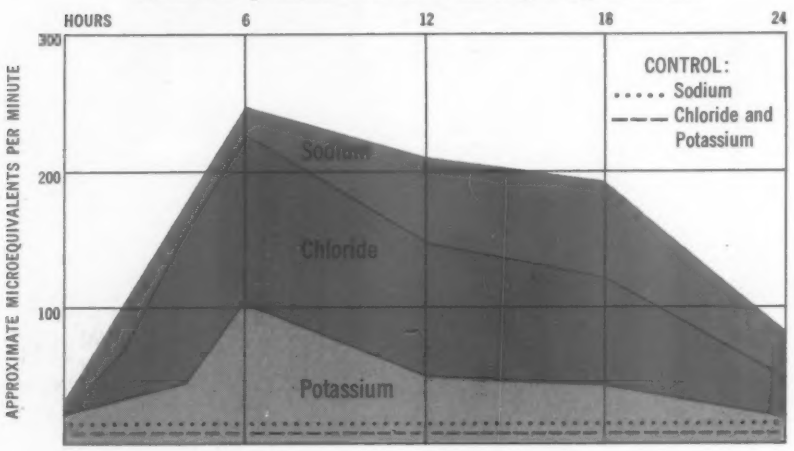
ABBOTT

104030A

# Every ENDURON tablet delivers over 24 hours of continuous thiazide action

With this unique agent, you need just *one* daily dose to reduce edema and hypertension. Diuretic response reaches maximum in about six hours. It then follows a smooth, continuing plateau for most of the remaining day. Even at end of the 24 hours, you are still eliminating sodium well above control (i.e., undosed) amounts.

**Usual Urinary Excretion Patterns Following 10 mg. of Enduron**




Note that Enduron's effect on urinary potassium is minor; potassium depletion will seldom be a factor in your therapy. Similarly, Enduron's favorably high ratio of sodium versus chloride excretion means lessened likelihood of hypochloremic alkalosis.

*How safe is Enduron?*

Repeated oral doses of many thousand times the therapeutic amount, have been well tolerated in test animals for months. Since Enduron's milligram dosage in humans is low, it affords the security of an exceptionally safe therapeutic ratio.

Difficulty, if any, is apt to arise from therapy that's unnecessarily vigorous. Enduron is potent. 10 mg. produces at least as much sodium excretion as other available thiazides in *any* size dose. Single doses greater than 10 mg. don't accomplish greater diuresis, and aren't recommended or needed.


Prescribe the 24-hour diuretic-antihypertensive:

# ENDURON

(METHYCLOTHIAZIDE, ABBOTT)

significant advance in thiazide therapy

ABBOTT

1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.



1040308

# NEW 8th EDITION

# 8 MODERN DRUG ENCYCLOPEDIA

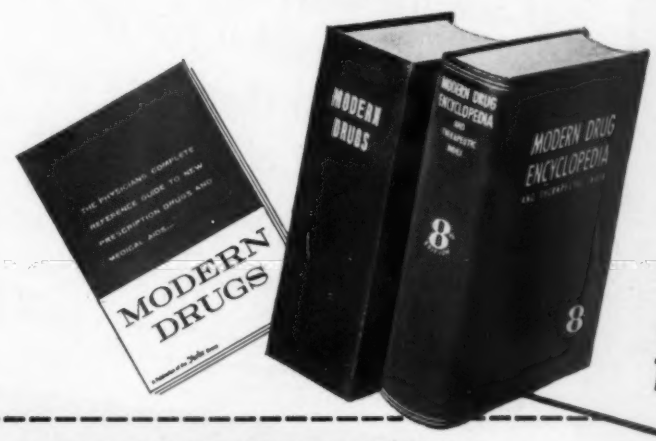
and Therapeutic Index with monthly supplement MODERN DRUGS

*The only complete reference on new as well as established products.*

*Quickly answers questions about ethical pharmaceuticals.*

**MODERN DRUG ENCYCLOPEDIA,** 8th Edition, an authoritative source of information on new and established pharmaceuticals. Gives you pertinent *facts* in concise form. Supplies facts you want to know to prescribe the new products with confidence. No struggle to keep cumbersome files up to date—just one compact bound volume and a compact binder for the monthly supplements.

**MODERN DRUGS** A monthly supplement, with Robert S. Goodhart, M.D. as supervising editor, and John C. Helenore, Ph.G. as technical editor, supplies the same complete information on *new* pharmaceuticals as soon as they are available on your prescription. A convenient binder keeps the 24 issues together. Cumulative indices in *each* issue help you find *any* product listed in previous months.




**THE PHYSICIAN'S REFERENCE LIBRARY IN ONE VOLUME KEPT UP-TO-DATE MONTHLY**

***ORDER YOUR MODERN DRUG ENCYCLOPEDIA TODAY***

**The Reuben H. Donnelley Corp., Publisher**
**MODERN DRUG ENCYCLOPEDIA**
**466 Lexington Avenue, New York 17, N.Y.**

☐ Enclosed is $17.50* for my 8th Edition of MODERN DRUG ENCYCLOPEDIA and Therapeutic Index and the Monthly Supplement—MODERN DRUGS.

☐ Enclosed also is $3.50 for binder for MODERN DRUGS Monthly Supplement.

For delivery in N.Y.C., please include 3% Sales Tax with remittance.

Name_____

Address_____

City_____ Zone_____ State_____

U.S.A. $17.50 Foreign $23.50 (U.S. Currency)

Please make checks payable to The Reuben H. Donnelley Corporation

*Includes 2-year supplementary service at $5.00 per year ($6.00 Foreign)

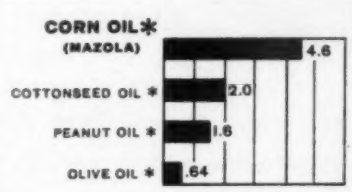
Of all leading brands
of vegetable oils...

# Mazola® liquid corn oil is best for replacing saturated fats

because Mazola is both unexcelled in polyunsaturates (that reduce serum cholesterol) and lowest in saturates (that raise serum cholesterol).

**HERE'S PROOF:**

This chart shows that the ratio of polyunsaturates to saturates provided by Mazola Corn Oil is more than twice that of any other leading vegetable oil.




*U. S. Dept. of Agriculture Reports—1959

Your patients will find Mazola Corn Oil ideally suited for salad dressings, baking and frying. By instructing them to use Mazola in place of a substantial portion of more saturated types of fat, and to watch their caloric intake, you frequently will be able to lower the serum cholesterol with minimum changes in eating habits.

MAZOLA CORN OIL IS ALSO AVAILABLE IN CANADA, WESTERN EUROPE, LATIN AMERICA AND MANY OTHER COUNTRIES THROUGHOUT THE WORLD


**COMPOSITION OF MAZOLA CORN OIL**

Mazola Corn Oil has the following average composition:

| Fatty Acids | Grams/ 100 grams | Grams/ fl. oz. (2 tablespoons) |
|---|---|---|
| Polyunsaturates... | 52-58 | 14-15.7 |
| Monounsaturates.. | 28-36 | 7.5-9.7 |
| Saturates ..... | 10-14 | 2.8-3.8 |
| Natural Sitosterols... | 1 (0.9-1.3) | 0.14 |
| Natural Tocopherols.. | about 0.1 | 0.015 |
| Cholesterol ..... | none | none |
| Salt (Sodium chloride) | none | none |

Calories—125/tablespoon
Iodine value—124 average

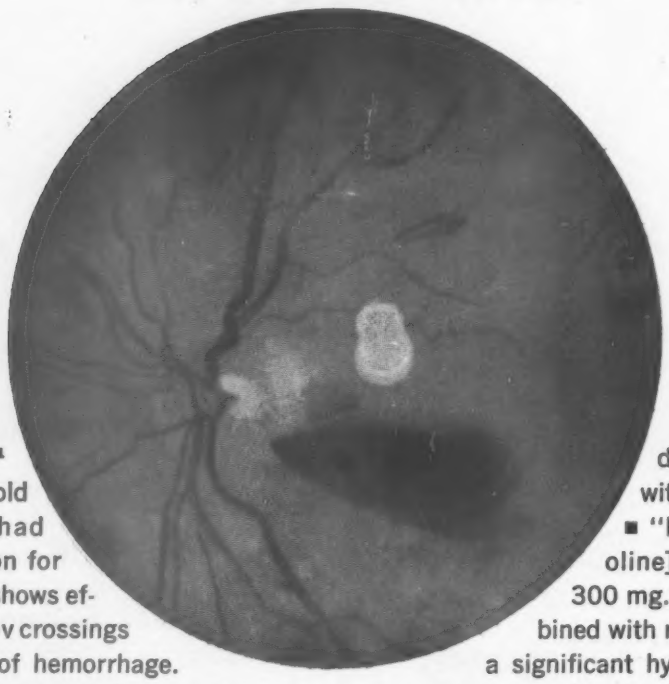
CORN OIL CONTINUES TO BE A PREFERRED VEGETABLE OIL IN NUTRITIONAL STUDIES OF HYPERCHOLESTEROLEMIA.

**FREE!**

Valuable aid for guiding your hypercholesterolemic patient in dietary control: **A Pad of Menu Guides** based on 2,000 calories per day, with which you may readily construct a diet pattern best suited to your patient's needs.

*Just write on your letterhead to:*
**CORN PRODUCTS COMPANY,**
**10 EAST 56 STREET, NEW YORK 22, N. Y.**

# When blood pressure must come down



**AS IN THIS CASE:**[1] Fundus of 62-year-old female who has had severe hypertension for many years. Photo shows effect of pressure at a-v crossings and various types of hemorrhage.

■ When you see eyeground changes like this—with such hypertensive symptoms as dizziness and headache—your patient is a candidate for Serpasil-Apresoline. With this combination the antihypertensive action of Serpasil complements that of Apresoline to bring blood pressure down to near-normal levels in many cases. Side effects can be reduced to a minimum, since Apresoline is effective in lower dosage when given with Serpasil.

■ "Hydralazine [Apresoline] in daily doses of 300 mg. or less, when combined with reserpine, produced a significant hypotensive effect in a large majority of our patients with fixed hypertension of over three years' duration."[2]

Complete information sent on request.

**SUPPLIED:** Tablets #2 (standard-strength), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride. Tablets #1 (half-strength), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride. /2832 HK

1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

## Serpasil®-Apresoline®

hydrochloride

(reserpine and hydralazine hydrochloride CIBA)

CIBA
SUMMIT, N. J.

# Advertisers' Product Index

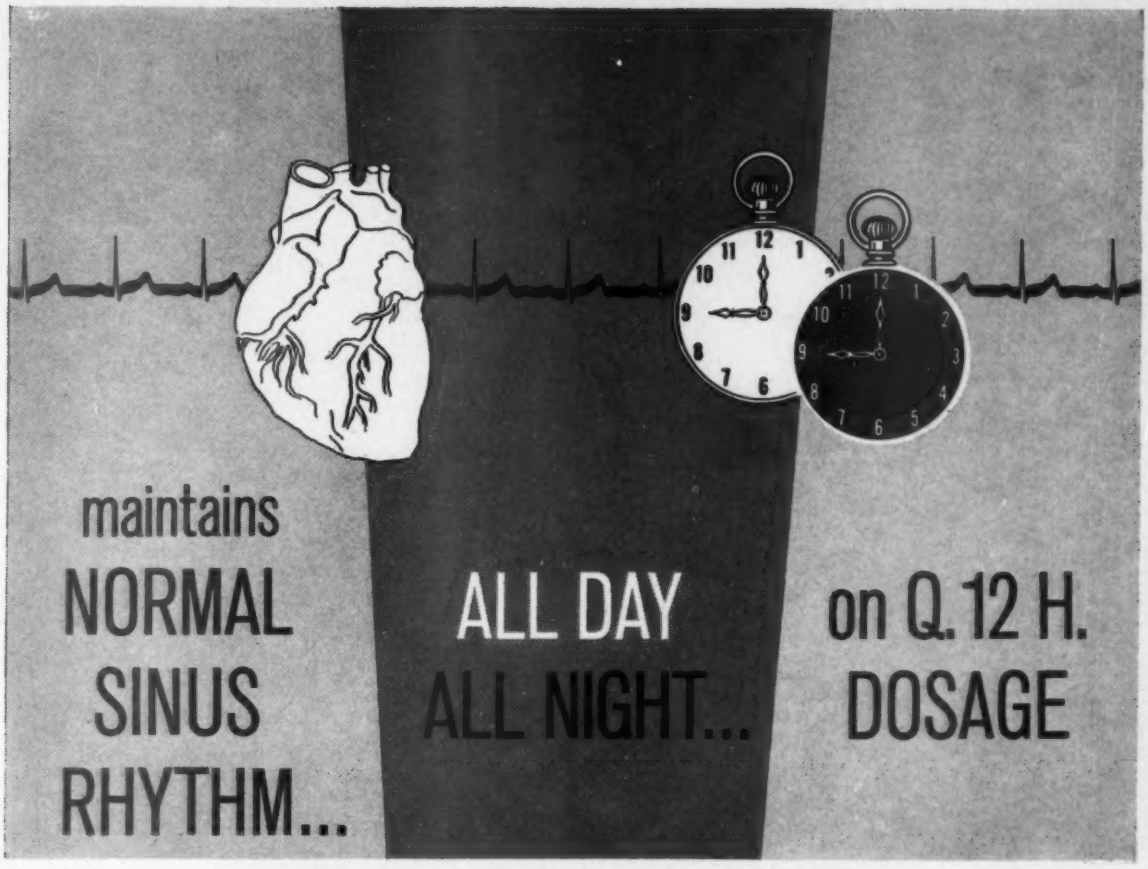
## June, 1961



**(Continued on next page)**

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

* Complete description of starred drugs will be found in
MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA




# QUINAGLUTE®

## DURA-TABS®

exclusive oral Sustained Medication*
Quinidine Gluconate 5 gr. (0.33 Gm.)

## IN CARDIAC ARRHYTHMIAS[1-10]

**Maximum efficacy:** maintains effective quinidine blood levels all day, all night. **Better tolerated:** because quinidine gluconate is 10 times as soluble as the sulfate, and only part of daily Dura-Tab dosage contacts gastric mucosa. **Maximum convenience:** given q. 12 h.—no night dosage needed.

**DOSAGE: for conversion** of auricular fibrillation to normal sinus rhythm, in most cases, 2 Dura-Tabs 3 or 4 times a day, for 2 to 3 days; longer periods are required in some patients. **For maintenance,** 2 Dura-Tabs q. 12 h. in most patients . . . Bottles of 30, 100 and 250 Quinaglute Dura-Tabs.

For SAMPLES and complete literature[1-10] giving indications, cautions, etc., write

REFER TO PDR Page 821

**WYNN PHARMACAL CORPORATION**

Lancaster Ave. at 51st St., Philadelphia, Pa.

*U.S. Patent 2,895,881

also available INJECTABLE QUINAGLUTE

SEE US at Booth #W-31 — AMERICAN MEDICAL ASSN. ANNUAL MEETING — June 25–30 — New York City

# When the rhythm is wrong...PRONESTYL® HYDROCHLORIDE

"Procaine amide [Pronestyl] should be [a] drug of choice in arrhythmias of ventricular origin."[1] "Pronestyl will be [a] drug of choice for intravenous use. The intramuscular preparation of Pronestyl has a clear advantage over the intramuscular preparation of quinidine because effects develop more rapidly."[2] Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3,4]... Pronestyl may be used in patients sensitive to quinidine... more prolonged action, less toxicity, less hypotensive effect than procaine... no CNS stimulation such as procaine may produce.

**Supply:** For convenient oral administration: Capsules, 0.25 Gm., in bottles of 100 and 1000. For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc. For full information see your Squibb Product Reference or Product Brief.

References: 1. Zozaya Cruz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C. V. Mosby Co., St. Louis, 1960, p. 419. 3. Kaydan, N., et al.: Am. Cardiovasc. Surgeons, Oct. 20, 1960. 4. Miller, M., et al.: J.A.M.A. 148:1004, 1952.

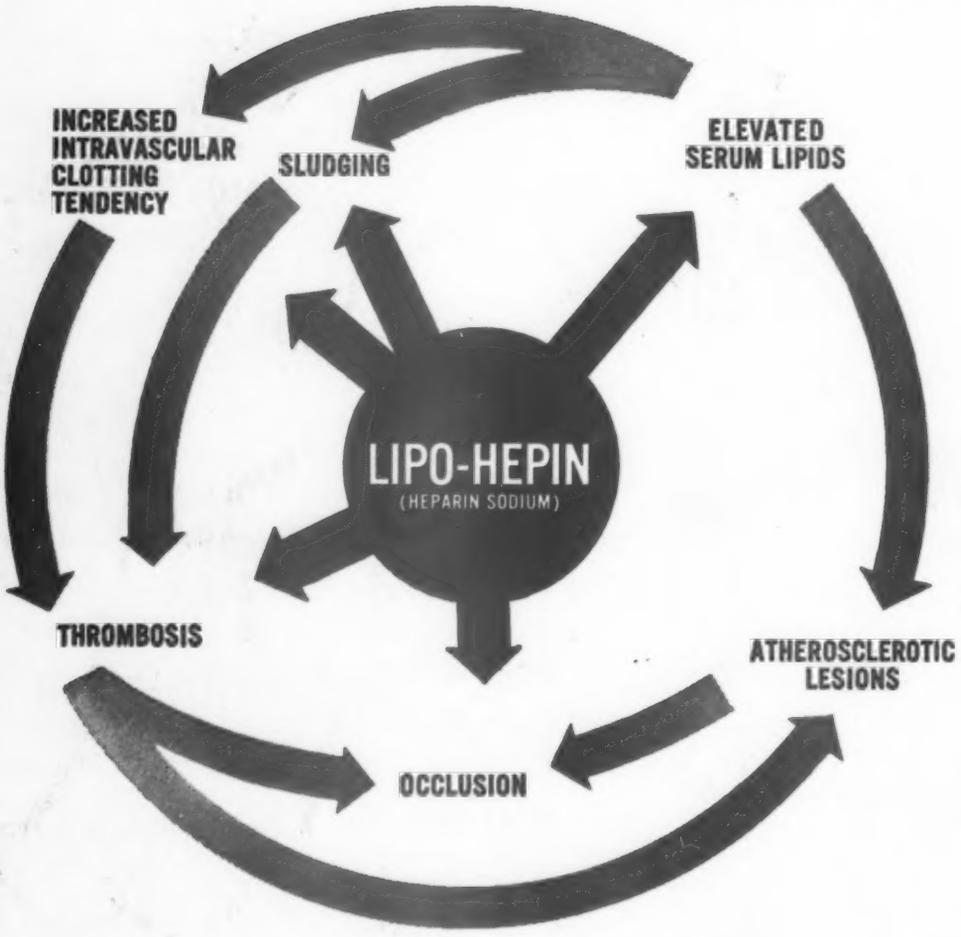
SQUIBB *Squibb Quality—the Priceless Ingredient*

## Positive Antithrombotic Therapy

# HEPARIN

is the only substance that protects against the organization and extension of thrombi by acting on both the clotting mechanism and on elevated lipid levels.

There is a growing body of evidence for inter-relationships among elevated serum lipids, atherosclerosis, hypercoagulability, and thrombosis.




# LIPO-HEPIN

HEPARIN SODIUM INJECTION, AQUEOUS

RIKER LABORATORIES, INC.
NORTHRIDGE, CALIFORNIA